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                  substances identified in English-, French-, German-,
                  and Japanese-language basic patents from 2004-present
 NEWS  3  NOV 26  MARPAT enhanced with FSORT command
 NEWS  4  NOV 26  CHEMSAFE now available on STN Easy
 NEWS  5  NOV 26  Two new SET commands increase convenience of STN
                  searching
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 NEWS  7  DEC 12  GBFULL now offers single source for full-text
                  coverage of complete UK patent families
 NEWS  8  DEC 17  Fifty-one pharmaceutical ingredients added to PS
 NEWS  9  JAN 06  The retention policy for unread STNmail messages
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 NEWS 10  JAN 07  WPIDS, WPINDEX, and WPIX enhanced Japanese Patent
                  Classification Data
 NEWS 11  FEB 02  Simultaneous left and right truncation (SLART) added
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 NEWS 12  FEB 02  GENBANK enhanced with SET PLURALS and SET SPELLING
 NEWS 13  FEB 06  Patent sequence location (PSL) data added to USGENE
 NEWS 14  FEB 10  COMPENDEX reloaded and enhanced
 NEWS 15  FEB 11  WTEXTILES reloaded and enhanced
 NEWS 16  FEB 19  New patent-examiner citations in 300,000 CA/CAplus
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 NEWS 18  FEB 23  Several formats for image display and print options
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                  and 2009 MeSH terms
 NEWS 20  FEB 23  TOXCENTER updates mirror those of MEDLINE - more
                  precise author group fields and 2009 MeSH terms
 NEWS 21  FEB 23  Three million new patent records blast AEROSPACE into
                  STN patent clusters

 NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
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=> file caplus medline

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FULL ESTIMATED COST	0.22	0.22

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FILE 'MEDLINE' ENTERED AT 14:18:31 ON 23 FEB 2009

=> s adenylyl cyclase
L1 16549 ADENYLYL CYCLASE

=> s l1 and parasit? and fung?
L2 8 L1 AND PARASIT? AND FUNG?

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 5 DUP REM L2 (3 DUPLICATES REMOVED)

=> d l3 ibib abs 1-5

L3 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:883136 CAPLUS
DOCUMENT NUMBER: 149:191969
TITLE: Adenylyl cyclases as novel targets for the treatment of infection by eukaryotic pathogens
INVENTOR(S): Levin, Lonny; Buck, Jochen; Brizuela, Leo; Pinnisi, Michael
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 111pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008088771	A2	20080724	WO 2008-US447	20080111

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,

TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2007-880089P P 20070112
AB The invention provides a method for preventing or treating a disease caused by infection by a eukaryotic pathogen, wherein the method comprises administering an effective amount of a modulator of a eukaryotic pathogen's adenylyl cyclase. The invention also provides pharmaceutical compns. useful for preventing or treating a disease, with the compns. containing a therapeutically effective amount of a modulator of a eukaryotic pathogen's adenylyl cyclase. The invention also provides screening methods for identifying selective modulators of a eukaryotic pathogen's adenylyl cyclase that do not substantially modulate an adenylyl cyclase of the subject. The invention also provides methods for culturing eukaryotic pathogens and methods for inducing the pathogenic state in vitro.

L3 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:481606 CAPLUS
DOCUMENT NUMBER: 137:291478
TITLE: A G-protein β subunit required for sexual and vegetative development and maintenance of normal Gα protein levels in Neurospora crassa
AUTHOR(S): Yang, Qi; Poole, Sheven I.; Borkovich, Katherine A.
CORPORATE SOURCE: Dep. Microbiology Molecular Genetics, Univ. Texas-Houston Med. Sch., Houston, TX, 77030, USA
SOURCE: Eukaryotic Cell (2002), 1(3), 378-390
CODEN: ECUEA2; ISSN: 1535-9778
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The genome of the filamentous fungus Neurospora crassa contains a single gene encoding a heterotrimeric G-protein β subunit, gnb-1. The predicted GNB-1 protein sequence is most identical to Gβ proteins from the filamentous fungi Cryphonectria parasitica and Aspergillus nidulans. N. crassa GNB-1 is also 65% identical to the human GNB-1 protein but only 38 and 45% identical to Gβ proteins from budding and fission yeasts. Previous studies in animal and fungal systems have elucidated phenotypes of Gβ null mutants, but little is known about the effects of Gβ loss on Gα levels. In this study, we analyzed a gnb-1 deletion mutant for cellular phenotypes and levels of the three Gα proteins. ΔGnb-1 strains are female-sterile, with production of aberrant fertilized reproductive structures. ΔGnb-1 strains conidiate more profusely and have altered mass on solid medium. Loss of gnb-1 leads to inappropriate conidiation and expression of a conidiation-specific gene during growth in submerged culture. Intracellular cAMP levels are reduced by 60% in vegetative plate cultures of Δgnb-1 mutants. Loss of gnb-1 leads to lower levels of the three Gα proteins under a variety of conditions. Anal. of transcript levels for the gna-1 and gna-2 Gα genes in submerged cultures indicates that regulation of Gα protein levels by gnb-1 is posttranscriptional. The results suggest that GNB-1 directly regulates apical extension rate and mass accumulation. In contrast, many other Δgnb-1 phenotypes, including female sterility and defective conidiation, can be explained by altered levels of the three N. crassa Gα proteins.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2000:722163 CAPLUS
DOCUMENT NUMBER: 134:15014
TITLE: Regulation of conidiation and adenylyl

cyclase levels by the Gα protein GNA-3 in Neurospora crassa

AUTHOR(S): Kays, Ann M.; Rowley, Patricia S.; Baasiri, Rudeina A.; Borkovich, Katherine A.

CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, University of Texas-Houston Medical School, Houston, TX, 77030, USA

SOURCE: Molecular and Cellular Biology (2000), 20(20), 7693-7705
CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have identified a new gene encoding the G protein α subunit, gna-3, from the filamentous fungus Neurospora crassa. The predicted amino acid sequence of GNA-3 is most similar to the Gα proteins MOD-D, MAGA, and CPG-2 from the saprophytic fungus Podospora anserina and the pathogenic fungi Magnaporthe grisea and Cryphonectria parasitica, resp. Deletion of gna-3 leads to shorter aerial hyphae and premature, dense conidiation during growth on solid medium or in standing liquid cultures and to inappropriate conidiation in submerged culture. The conidiation and aerial hypha defects of the Δgna-3 strain are similar to those of a previously characterized adenylyl cyclase mutant, cr-1. Supplementation with cAMP restores wild-type morphol. to Δgna-3 strains in standing liquid cultures. Solid medium augmented with exogenous cAMP suppresses the premature conidiation defect, but aerial hypha formation is still reduced. Submerged-culture conidiation is refractory to cAMP but is suppressed by peptone. In addition, Δgna-3 submerged cultures express the glucose-repressible gene, qa-2, to levels greatly exceeding those observed in the wild type under carbon-starved conditions. ΔGna-3 strains exhibit reduced fertility in homozygous crosses during the sexual cycle; exogenous cAMP has no effect on this phenotype. Intracellular steady-state cAMP levels of Δgna-3 strains are decreased 90% relative to the wild type under a variety of growth conditions. Reduced intracellular cAMP levels in the Δgna-3 strain correlate with lower adenylyl cyclase activity and protein levels. These results demonstrate that GNA-3 modulates conidiation and adenylyl cyclase levels in N. crassa.

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 1998:17931 CAPLUS

DOCUMENT NUMBER: 128:136984

ORIGINAL REFERENCE NO.: 128:26827a,26830a

TITLE: Fil1, a G-protein α-subunit that acts upstream of cAMP and is essential for dimorphic switching in haploid cells of Ustilago hordei

AUTHOR(S): Lichter, A.; Mills, D.

CORPORATE SOURCE: Department of Botany and Plant Pathology, Oregon State University, Corvallis, OR, 97331-2902, USA

SOURCE: Molecular & General Genetics (1997), 256(4), 426-435
CODEN: MGGEAE; ISSN: 0026-8925

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A constitutive mutation, fil1, that causes filamentous growth in the haplophase of the dimorphic smut fungus Ustilago hordei, was previously shown to be genetically associated with a 50-kb deletion within a 940-kb chromosome. Physiol. studies suggested that a gene that functions upstream of adenylyl cyclase was deleted in the

mutant. Representational difference anal. of isolated chromosomes was used to obtain deletion-specific DNA probes and corresponding genomic cosmid clones. Complementation anal. identified a cosmid clone and subsequently a 2.1-kb insert that converted transformants of the mutant strain 10.1a(fil1) from the filamentous to the sporidial cell type. A single open reading frame of 354 codons that encodes a putative α-subunit of the heterotrimeric G-proteins was identified. Fil1 displayed a high degree of sequence identity to Gpa1 from the basidiomycete Cryptococcus neoformans and CPG-2 from the ascomycete Cryphonectria parasitica. FIL1, when introduced on a self-replicating vector, was found to suppress filamentous growth of starved haploid wild-type strains and restore normal mating response to the fil1 mutant, but did not suppress sexual dimorphism of either strain. Fil1 appears to function analogously to mammalian Gα proteins, which are coupled to cAMP production via adenylyl cyclase, to regulate dimorphic switching in U. hordei.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 1996:450887 CAPLUS
DOCUMENT NUMBER: 125:137665
ORIGINAL REFERENCE NO.: 125:25656h,25657a
TITLE: Extensive alteration of fungal gene transcript accumulation and elevation of G-protein-regulated cAMP levels by a virulence-attenuating hypovirus
AUTHOR(S): Chen, Baoshan; Gao, Shaojian; Choi, Gil H.; Nuss, Donald L.
CORPORATE SOURCE: Center Agricultural Biotechnology, University Maryland, College Park, MD, 20742-3351, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1996), 93(15), 7996-8000 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Persistent infection of the chestnut blight fungus Cryphonectria parasitica with the prototypic hypovirus CHV1-713 results in attenuation of fungal virulence (hypovirulence) and reduced accumulation of the GTP-binding (G) protein α subunit CPG-1. Transgenic cosuppression of CPG-1 accumulation in the absence of virus infection also confers hypovirulence. We now report the use of mRNA differential display to examine the extent to which virus infection alters fungal gene transcript accumulation and to assess the degree to which modification of CPG-1 signal transduction contributes to this alteration. More than 400 PCR products were identified that either increased (296 products) or decreased (127 products) in abundance as a result of virus infection. Significantly, 65% of these products exhibited similar changes as a result of CPG-1 cosuppression in the absence of virus infection. We also report that both virus infection and CPG-1 cosuppression elevate cAMP levels 3- to 5-fold. Addnl., it was possible to mimic the effect of virus infection and CPG-1 cosuppression on transcript accumulation for representative fungal genes by drug-induced elevation of cAMP levels. These results strengthen and extend previous indications that hypovirus infection causes a significant and persistent alteration of fungal gene expression/transcript accumulation. They further show that this alteration is primarily mediated through modification of the CPG-1 signaling pathway and suggest that, similar to mammalian Gi α subunits, CPG-1 functions as a neg. modulator of adenylyl cyclase. Finally, these results suggest a role for G-protein-regulated cAMP accumulation in

hypovirus-mediated alteration of fungal gene expression.

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NEWS	12	FEB 02	GENBANK enhanced with SET PLURALS and SET SPELLING
NEWS	13	FEB 06	Patent sequence location (PSL) data added to USGENE
NEWS	14	FEB 10	COMPENDEX reloaded and enhanced
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NEWS	16	FEB 19	New patent-examiner citations in 300,000 CA/CAplus patent records provide insights into related prior art
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NEWS	18	FEB 23	Several formats for image display and print options discontinued in USPATFULL and USPAT2
NEWS	19	FEB 23	MEDLINE now offers more precise author group fields and 2009 MeSH terms
NEWS	20	FEB 23	TOXCENTER updates mirror those of MEDLINE - more precise author group fields and 2009 MeSH terms
NEWS	21	FEB 23	Three million new patent records blast AEROSPACE into STN patent clusters

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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http://www.cas.org/support/stngen/stndoc/properties.html

=> e adenylyl

E1	1	ADENYLURIDYLGUAN/BI
E2	1	ADENYLURIDYLGUANOSINE/BI
E3	64797 -->	ADENYLYL/BI
E4	3	ADENYLYLADENOSINE/BI
E5	4	ADENYLYLAMINO/BI
E6	1	ADENYLYLASE/BI
E7	4	ADENYLYLATE/BI
E8	1	ADENYLYLATED/BI
E9	9	ADENYLYLATING/BI
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E11	1	ADENYLYLCARBON/BI
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=> e adenylylcyclase

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E2	1	ADENYLYLCARBONYLNITRILO/BI
E3	0 -->	ADENYLYLCYCLASE/BI
E4	2	ADENYLYLCYTIDYLYL/BI

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=> s (adenylyl cyclase or adenyl cyclase or adenylate cyclase)
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L3           9 L2 AND FUNG? AND PARASIT?

=> d l3 ibib abs 1-9

L3   ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2007:438578  CAPLUS
DOCUMENT NUMBER:         146:468443
TITLE:                   Methods and compositions for generating bioactive
                         assemblies of increased complexity and their
                         therapeutic and diagnostic uses
INVENTOR(S):             Chang, Chien Hsing; Goldenberg, David M.; McBride,
                         William J.; Rossi, Edmund A.
PATENT ASSIGNEE(S):      IBC Pharmaceuticals, Inc., USA
SOURCE:                  U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S.
                         Ser. No. 391,584.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  7
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
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     US 20070086942       A1    20070419    US 2006-478021          20060629
     US 20060228357       A1    20061012    US 2006-389358          20060324
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AU 2006330051 A1 20070705 AU 2006-330051 20061205
CA 2633486 A1 20070705 CA 2006-2633486 20061205
WO 2007075270 A2 20070705 WO 2006-US46367 20061205
WO 2007075270 A3 20080306
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,
KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

EP 1959993 A2 20080827 EP 2006-848816 20061205
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL,

BA, HR, MK, RS

KR 2008055932	A	20080619	KR 2008-709357		20080418
IN 2008DN03448	A	20080725	IN 2008-DN3448		20080425
IN 2008DN04630	A	20080815	IN 2008-DN4630		20080529
KR 2008097995	A	20081106	KR 2008-717349		20080716
PRIORITY APPLN. INFO.:			US 2005-728292P	P	20051019
			US 2005-751196P	P	20051216
			US 2006-782332P	P	20060314
			US 2006-389358	A2	20060324
			WO 2006-US10762	A	20060324
			US 2006-391584	A2	20060328
			WO 2006-US12084	A	20060329
			US 2005-668603P	P	20050406
			US 2006-478021	A2	20060629
			WO 2006-US25499	A2	20060629
			WO 2006-US40431	W	20061016
			US 2006-864530P	P	20061106
			WO 2006-US46367	W	20061205

AB The present invention concerns methods and compns. for making and using bioactive assemblies of defined compns., which may have multiple functionalities and/or binding specificities. In particular embodiments, the bioactive assembly is formed using dock-and-lock (DNL) methodol., which takes advantage of the specific binding interaction between dimerization and docking domains (DDD) and anchoring domains (AD) to form the assembly. In various embodiments, one or more effectors may be attached to a DDD or AD sequence. Complementary AD or DDD sequences may be attached to an adaptor module that forms the core of the bioactive assembly, allowing formation of the assembly through the specific DDD/AD binding interactions. Such assemblies may be attached to a wide variety of effector moieties for treatment, detection and/or diagnosis of a disease, pathogen infection or other medical or veterinary condition.

L3 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2005:902006 CAPLUS
DOCUMENT NUMBER:	143:242007
TITLE:	Use of metronidazole for the preparation of a pharmaceutical composition for treatment of pathologies associated with type-B interleukin 8 receptor and/or with PAC-1 receptor
INVENTOR(S):	Folfi, Fabrizio; Safonova, Irina
PATENT ASSIGNEE(S):	Galderma Research & Development, Fr.
SOURCE:	Fr. Demande, 24 pp. CODEN: FRXXBL
DOCUMENT TYPE:	Patent
LANGUAGE:	French
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2866569	A1	20050826	FR 2004-1721	20040220
FR 2866569	B1	20070824		
AU 2005224123	A1	20050929	AU 2005-224123	20050217
CA 2553932	A1	20050929	CA 2005-2553932	20050217
WO 2005089750	A2	20050929	WO 2005-FR370	20050217
WO 2005089750	A3	20060504		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1718296	A2	20061108	EP 2005-729371		20050217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU					
BR 2005006550	A	20070227	BR 2005-6550		20050217
CN 1921852	A	20070228	CN 2005-80005575		20050217
JP 2007523133	T	20070816	JP 2006-553618		20050217
MX 2006009314	A	20061009	MX 2006-9314		20060816
KR 2006124707	A	20061205	KR 2006-716588		20060818
IN 2006DN04754	A	20070831	IN 2006-DN4754		20060818
US 20080221189	A1	20080911	US 2007-590031		20070524
PRIORITY APPLN. INFO.:			FR 2004-1721	A	20040220
			WO 2005-FR370	W	20050217

AB Metronidazole is used for the preparation of a pharmaceutical compns. intended for the treatment of pathologies wherein at least IL-8RB and PAC-1 receptors are involved. Efficacy of metronidazole in inhibition of IL-8RB and PAC-1 receptors specific ligands is described.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:902002 CAPLUS
DOCUMENT NUMBER: 143:222567
TITLE: Use of a modulator of IL-8RB and/or PAC-1 for the treatment of rosacea
INVENTOR(S): Folfi, Fabrizio; Safonova, Irina
PATENT ASSIGNEE(S): Galderma Research & Development, Fr.
SOURCE: Fr. Demande, 16 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
FR 2866565	A1	20050826	FR 2004-1716		20040220
CA 2553188	A1	20050901	CA 2005-2553188		20050217
WO 2005079770	A2	20050901	WO 2005-FR366		20050217
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1718285	A2	20061108	EP 2005-729353		20050217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS					
US 20080033060	A1	20080207	US 2007-589991		20070817
PRIORITY APPLN. INFO.:			FR 2004-1716	A	20040220
			WO 2005-FR366	W	20050217

AB The invention discloses the use of a modulating compound of at least one

receptor chosen from IL-8RB and PAC-1 for the preparation of a pharmaceutical composition for the treatment of rosacea.

L3 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN

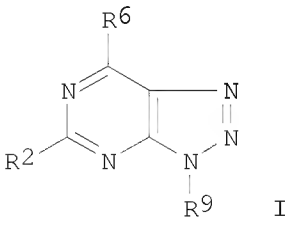
ACCESSION NUMBER:	2004:182882 CAPLUS
DOCUMENT NUMBER:	140:217666
TITLE:	Preparation of di- and tri-substituted 8-azapurine derivatives as cyclin-dependent kinase inhibitors
INVENTOR(S):	Fuksova, Kveta; Havlicek, Libor; Krystof, Vladimir; Lenobel, Rene; Strnad, Miroslav
PATENT ASSIGNEE(S):	Institute of Experimental Botany ASCR, Czech Rep.
SOURCE:	PCT Int. Appl., 143 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

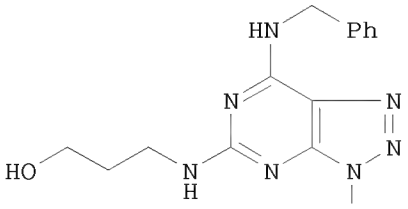
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004018473	A2	20040304	WO 2003-IB4188	20030822
WO 2004018473	A3	20040521		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003260919	A1	20040311	AU 2003-260919	20030822
EP 1539760	A2	20050615	EP 2003-792601	20030822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006511458	T	20060406	JP 2004-530478	20030822
US 20060035909	A1	20060216	US 2005-51059	20050204
PRIORITY APPLN. INFO.:			GB 2002-19746 A	20020823
			WO 2003-IB4188 W	20030822

OTHER SOURCE(S): MARPAT 140:217666

GI



I



II

AB Title compds. I [R6 = halo, NHNH2, amino, etc.; R2 = halo, NHNH2, alkyl, etc.; R9 = alkyl, cycloalkyl, etc.] are prepared For instance, 4-amino-5-carboxamido-1-isopropyl-1,2,3-triazole (preparation given) is converted to 2,6-dihydroxy-9-isopropyl-8-azapurine (EtOH, NaOEt, (EtO)2CO,

90°, 4 h). The dihydroxy derivative is converted to the corresponding dichloride (POCl3, lutidine, 120°, 3 h), treated with benzylamine (n-BuOH) followed by 3-aminopropanol to give II. II has IC50 = 54.6 μM for CDK2-cyclin E. The present invention relates to a compound of formula (I), or a pharmaceutically acceptable acid salt thereof. I are useful in the treatment of hyperproliferative skin disorders, viral infections, cancer, etc. The invention also relates to the use of 2,6,9-trisubstituted-8-azapurines in maintaining mammalian oocytes at the germinal vesicle stage.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

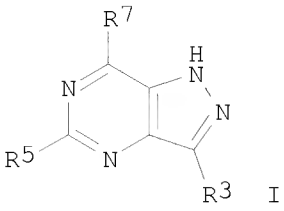
L3 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:771374 CAPLUS
DOCUMENT NUMBER: 139:292259
TITLE: Preparation of pyrazolo[4,3-d]pyrimidines as selective inhibitors of cyclin-dependent kinases, cell proliferation inhibitors, and apoptosis inducers for therapy of diseases
INVENTOR(S): Moravcova, Daniela; Havlicek, Libor; Krystof, Vladimir; Lenobel, Rene
PATENT ASSIGNEE(S): Ustav Experimentalni Botaniky Av Cr (Institute of Experimental Botany Academy of Sciences of the Czech Republic), Czech Rep.
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1348707	A1	20031001	EP 2002-7163	20020328
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2480409	A1	20031009	CA 2003-2480409	20030327
WO 2003082872	A1	20031009	WO 2003-EP3207	20030327
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003226731	A1	20031013	AU 2003-226731	20030327
AU 2003226731	B2	20080522		
JP 2005527565	T	20050915	JP 2003-580337	20030327
US 20050080097	A1	20050414	US 2004-952087	20040928

PRIORITY APPLN. INFO.:			
EP 2002-7163	A	20020328	
WO 2003-EP3207	W	20030327	

OTHER SOURCE(S): MARPAT 139:292259
GI



I

AB The invention relates to 3,5,7-trisubstituted pyrazolo[4,3-d]pyrimidines represented by the general formula (I) and pharmaceutically acceptable salts thereof [wherein R3 is an optionally substituted alkyl, cycloalkyl, cycloheteroalkyl, cycloalkyl alkyl, aryl or alkylaryl group; R5 = halogen, NHNH2, NHOH, NHCONH2, guanyl (NH-C(:NH)NH2) an optionally substituted C1-6 alkyl, alkenyl, alkynyl, C3-15 cycloalkyl, Rf(C3-15 cycloalkyl), heterocycle, heteroalkyl, aryl, heteroaryl, arylalkyl, cycloheteroalkyl, cycloheteroalkyl alkyl, heteroarylalkyl group, the group CORa, CONRbRc, SO3Rd, or NHC(O)Re [wherein Ra, Rf = optionally substituted C1-6 alkyl, alkenyl, or alkynyl; Rb, Rc, Rd = independently H, optionally substituted C1-6 alkyl, alkenyl, or alkynyl; Re = HO, amino, alkoxy, alkylamino, optionally substituted C1-6 alkyl, alkenyl or alkynyl group, or X-R5' [wherein X = NH, O, S or N(alkyl) and R5' = H, optionally substituted C1-6 alkyl, alkenyl, alkynyl, C3-15 cycloalkyl, Rf(C3-15 cycloalkyl), aryl, heterocycle, hetero C1-6 alkyl, arylalkyl, heteroaryl, cycloheteroalkyl, cycloheteroalkyl alkyl, or heteroarylalkyl, the group CORa, CONRbRc, SO3Rd, or NHCORe, wherein Ra, Rb, Rc, Rd, Re and Rf have the above meaning]]; R7 = halogen, NHNH2, NHOH, NHCONH2, guanyl(NH-C(:NH)NH2) or the group X-R7', wherein X has the above meaning of R7' is as defined for R5']. These compds. are useful for treating cancer, or psoriasis, rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, restenosis, polycystic kidney disease, graft rejection, graft vs. host disease and gout, parasitoses such as those caused by fungi or protists, or Alzheimer's disease, or as antineurogenerative drugs, or to suppress immunostimulation. They are also used for treating an hyperproliferative skin disease in a human suffering therefrom by actinic keratosis, Bowen's disease, papilloma, seborrheic keratosis, toxic eczema, atopic dermatitis and ichthyosis. They modulate the activation of adrenergic and/or purinergic receptors which as a consequence result in the activation or inactivation of adenylate cyclase in cancer, asthma, cardiovascular, neurodegenerative and inflammatory diseases. Also disclosed are (1) a method of eliminating or reducing viral spread or growth in tissue culture systems during the production of biopharmaceutical or other products such as proteins and vaccines, for elimination or reduction of viral spread and growth in clin. samples such as blood, and for stopping of growth of tissue culture cells while leaving the cells to carry on with protein and secondary products (antibiotics, secondary plant products, and the like) production, using the compds. I, (2) a method of suppressing immunostimulation (e.g. arthritis or in suppression of transplant rejection) in mammals by administration of I, (3) a method of inducing apoptosis in mammalian cells by administration of I, (4) a method of inhibiting aging and senescence of mammalian cells, the health and youthful appearance of skin and body using I, and (5) a method of maintaining mammalian oocytes at the germinal vesicle stage and their fertilization during mammalian cloning processes by using I. Disclosed is a method of treating viral infections, in particular those caused by DNA viruses including herpesviruses HSV- 1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-7, HHV-8 or vaccinia virus, papilloma viruses, flaviviruses, retroviruses, adenoviruses, cytomegalovirus, and the like.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:344861 CAPLUS
DOCUMENT NUMBER: 131:4240
TITLE: Immunoglobulin molecules having a synthetic variable region and modified specificity
INVENTOR(S): Burch, Ronald M.
PATENT ASSIGNEE(S): Euro-Celtique, S.A., Bermuda
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925378	A1	19990527	WO 1998-US24302	19981113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2309990	A1	19990527	CA 1998-2309990	19981113
CA 2310269	A1	19990527	CA 1998-2310269	19981113
WO 9925379	A1	19990527	WO 1998-US24303	19981113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9914597	A	19990607	AU 1999-14597	19981113
AU 763029	B2	20030710		
AU 9914598	A	19990607	AU 1999-14598	19981113
AU 737457	B2	20010823		
EP 1030684	A1	20000830	EP 1998-958584	19981113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1032420	A1	20000906	EP 1998-958583	19981113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001526021	T	20011218	JP 2000-520811	19981113
BR 9815289	A	20011226	BR 1998-15289	19981113
BR 9815580	A	20020129	BR 1998-15580	19981113
JP 2002507544	T	20020312	JP 2000-520812	19981113
ZA 9900048	A	19990708	ZA 1999-48	19990105
ZA 9900049	A	20000309	ZA 1999-49	19990105
IN 1999MA00037	A	20050304	IN 1999-MA37	19990107
IN 1999MA00038	A	20050304	IN 1999-MA38	19990107
MX 2000004582	A	20010930	MX 2000-4582	20000512
MX 2000004581	A	20011011	MX 2000-4581	20000512
US 20020028469	A1	20020307	US 2001-963232	20010926
AU 2003252902	A1	20031106	AU 2003-252902	20031010
PRIORITY APPLN. INFO.:			US 1997-65716P P	19971114
			US 1998-81403P P	19980410

US 1998-191780	A1	19981113
WO 1998-US24302	W	19981113
WO 1998-US24303	W	19981113

AB The invention provides modified Ig mols., particularly antibodies, that immunospecifically bind a first member of a binding pair which binding pair consists of the first member and a second member, which Igs have a variable domain containing one or more complimentary determining regions that contain the amino acid sequence of a binding site for the second member of the binding pair. The first member is a tumor antigen or an antigen of an infectious disease agent, and the second member is a mol. on the surface of an immune cell. The invention further provides for therapeutic and diagnostic use of the modified Ig.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1996:450887 CAPLUS
DOCUMENT NUMBER: 125:137665
ORIGINAL REFERENCE NO.: 125:25656h,25657a
TITLE: Extensive alteration of fungal gene transcript accumulation and elevation of G-protein-regulated cAMP levels by a virulence-attenuating hypovirus
AUTHOR(S): Chen, Baoshan; Gao, Shaojian; Choi, Gil H.; Nuss, Donald L.
CORPORATE SOURCE: Center Agricultural Biotechnology, University Maryland, College Park, MD, 20742-3351, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1996), 93(15), 7996-8000 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Persistent infection of the chestnut blight fungus Cryphonectria parasitica with the prototypic hypovirus CHV1-713 results in attenuation of fungal virulence (hypovirulence) and reduced accumulation of the GTP-binding (G) protein α subunit CPG-1. Transgenic cosuppression of CPG-1 accumulation in the absence of virus infection also confers hypovirulence. We now report the use of mRNA differential display to examine the extent to which virus infection alters fungal gene transcript accumulation and to assess the degree to which modification of CPG-1 signal transduction contributes to this alteration. More than 400 PCR products were identified that either increased (296 products) or decreased (127 products) in abundance as a result of virus infection. Significantly, 65% of these products exhibited similar changes as a result of CPG-1 cosuppression in the absence of virus infection. We also report that both virus infection and CPG-1 cosuppression elevate cAMP levels 3- to 5-fold. Addnl., it was possible to mimic the effect of virus infection and CPG-1 cosuppression on transcript accumulation for representative fungal genes by drug-induced elevation of cAMP levels. These results strengthen and extend previous indications that hypovirus infection causes a significant and persistent alteration of fungal gene expression/transcript accumulation. They further show that this alteration is primarily mediated through modification of the CPG-1 signaling pathway and suggest that, similar to mammalian Gi α subunits, CPG-1 functions as a neg. modulator of adenylyl cyclase. Finally, these results suggest a role for G-protein-regulated cAMP accumulation in hypovirus-mediated alteration of fungal gene expression.

L3 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1995:303419 CAPLUS

DOCUMENT NUMBER: 122:76220
ORIGINAL REFERENCE NO.: 122:14379a,14382a
TITLE: Virus-mediated or transgenic suppression of a G-protein α subunit and attenuation of fungal virulence
AUTHOR(S): Choi, Gil H.; Chen, Baoshan; Nuss, Donald L.
CORPORATE SOURCE: Roche Institute Molecular Biology, Roche Research Center, Nutley, NJ, 07110, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(1), 305-9
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Strains of the chestnut blight fungus Cryphonectria parasitica parasitica harboring RNA viruses of the genus Hypovirus exhibit significantly reduced levels of virulence (called hypovirulence). The accumulation of a heterotrimeric GTP-binding protein (G protein) α subunit of the Gi class was found to be reduced in hypovirus-containing C. parasitica strains. Transgenic cosuppression, a phenomenon frequently observed in transgenic plants, reduced the accumulation of this α subunit in virus-free fungal strains. Significantly, the resulting transgenic fungal strains were also hypovirulent. These results indicate a crucial role for G-protein-linked signal transduction in fungal pathogenesis and suggest a mol. basis for virus-mediated attenuation of fungal virulence.

L3 ANSWER 9 OF 9 CAPLUS
ACCESSION NUMBER: 1989:455685 CAPLUS
DOCUMENT NUMBER: 111:55685
ORIGINAL REFERENCE NO.: 111:9461a,9464a
TITLE: Avirulent microbe vaccines lacking functional adenylate cyclase and cAMP receptor protein, their preparation, and uses therefor
INVENTOR(S): Curtiss, Roy, III
PATENT ASSIGNEE(S): Molecular Engineering Associates, Inc., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8809669	A1	19881215	WO 1988-US1899	19880601
W: AU, DK, JP, KR				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8819550	A	19890104	AU 1988-19550	19880601
AU 623599	B2	19920521		
EP 315682	A1	19890517	EP 1988-905542	19880601
EP 315682	B1	19931222		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 01503442	T	19891122	JP 1988-505197	19880601
JP 2640525	B2	19970813		
AT 98870	T	19940115	AT 1988-905542	19880601
CA 1338957	C	19970304	CA 1988-568456	19880602
ZA 8803954	A	19890222	ZA 1988-3954	19880603
CN 1030018	A	19890104	CN 1988-104317	19880604
CN 1034553	C	19970416		
DK 8900527	A	19890203	DK 1989-527	19890203

DK 175512	B1	20041115			
KR 139950	B1	19980601	KR 1989-700206		19890204
US 5294441	A	19940315	US 1991-785748		19911107
WO 9208486	A1	19920529	WO 1991-US8376		19911108
W: AU, CA, JP					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE					
AU 9191204	A	19920611	AU 1991-91204		19911108
AU 666108	B2	19960201			
ZA 9108876	A	19920826	ZA 1991-8876		19911108
EP 556333	A1	19930825	EP 1992-901722		19911108
EP 556333	B1	20030319			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE					
JP 06501849	T	19940303	JP 1992-502265		19911108
JP 3601602	B2	20041215			
IL 100010	A	19980208	IL 1991-100010		19911108
CA 2095534	C	20020917	CA 1991-2095534		19911108
AT 234917	T	20030415	AT 1992-901722		19911108
EP 1323428	A2	20030702	EP 2003-6123		19911108
EP 1323428	A3	20030917			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE					
ES 2194837	T3	20031201	ES 1992-901722		19911108
CN 1063416	A	19920812	CN 1991-111876		19911109
US 5389368	A	19950214	US 1992-965607		19921022
US 5468485	A	19951121	US 1993-20259		19930218
US 5387744	A	19950207	US 1993-88394		19930707
US 5855879	A	19990105	US 1994-209542		19940310
US 5855880	A	19990105	US 1996-596732		19960205
JP 2004337175	A	20041202	JP 2004-207489		20040714
PRIORITY APPLN. INFO.:			US 1987-58360	A	19870604
			US 1988-200934		19880601
			US 1990-612001		19901109
			US 1987-106072	B2	19871007
			EP 1988-905542	A	19880601
			WO 1988-US1899	A	19880601
			US 1988-251304	B2	19881003
			US 1989-332285	B1	19890331
			US 1991-785748	A3	19911107
			EP 1992-901722	A3	19911108
			JP 1992-502265	A3	19911108
			WO 1991-US8376	A	19911108
			US 1992-975892	B1	19921113
			US 1994-209542	A3	19940310

AB A vaccine for immunization of vertebrates or invertebrates comprises an avirulent derivative of a pathogen that is incapable of producing functional adenylate cyclase (AC) and cAMP receptor protein (cRP). The avirulent microbe is produced by recombinant DNA techniques or transposon mutagenesis, forming deletion mutations in each of the genes for AC and cRP. The avirulent microbe is also used as a carrier for synthesis of a vertebrate or invertebrate host protein to produce a product capable of suppressing, modulating, or augmenting immunity. Mice inoculated with avirulent transposon Tn10-mutagenized Salmonella typhimurium, χ 4062 and χ 4064 (Δcya-3 Δcrp-2 and Δcya-1 Δcrp-1, resp.), survived subsequent peroral challenge with 104 times the LD50 of fully virulent S. typhimurium SR11 χ 3306.

=> l2 and (antifung? or antiparasit? or antimicrob?)
L2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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=> s l2 and (antifung? or antiparasit? or antimicrob?)
L4          61 L2 AND (ANTIFUNG? OR ANTIPARASIT? OR ANTIMICROB?)

=> d l4 ibib abs 1-61

L4   ANSWER 1 OF 61  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2009:71349  CAPLUS
TITLE:                   Structure and Inhibition of the CO2-Sensing
                         Carbonic Anhydrase Can2 from the Pathogenic Fungus
                         Cryptococcus neoformans
AUTHOR(S):               Schlicker, Christine; Hall, Rebecca A.; Vullo,
                         Daniela; Middelhaufe, Sabine; Gertz, Melanie; Supuran,
                         Claudiu T.; Muehlschlegel, Fritz A.; Steegborn,
                         Clemens
CORPORATE SOURCE:        Department of Physiological Chemistry, Ruhr-University
                         Bochum, Bochum, 44801, Germany
SOURCE:                  Journal of Molecular Biology (2009), 385(4), 1207-1220
                         CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER:               Elsevier Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   In the pathogenic fungus Cryptococcus neoformans, a CO2-sensing system is
     essential for survival in the natural environment (.apprx. 0.03% CO2) and
     mediates the switch to virulent growth in the human host (.apprx. 5% CO2).
     This system is composed of the carbonic anhydrase (CA) Can2, which
     catalyzes formation of bicarbonate, and the fungal, bicarbonate-stimulated
     adenylyl cyclase Cac1.  The critical role of these enzymes
     for fungal metabolism and pathogenesis identifies them as targets for
     antifungal drugs.  Here, we prove functional similarity of Can2 to
     the CA Nce103 from Candida albicans and describe its biochem. and
     structural characterization.  The crystal structure of Can2 reveals that
     the enzyme belongs to the "plant-type" β-CAs but carries a unique
     N-terminal extension that can interact with the active-site entrance of
     the dimer.  We further tested a panel of compds., identifying nanomolar
     Can2 inhibitors, and present the structure of a Can2 complex
     with the inhibitor and product analog acetate, revealing
     insights into interactions with physiol. ligands and inhibitors.

L4   ANSWER 2 OF 61  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2008:1530060  CAPLUS
DOCUMENT NUMBER:         150:71089
TITLE:                   Cyclic AMP-elevating or -mimicking agents for the
                         treatment of urinary tract infections
INVENTOR(S):             Abraham, Soman N.; Bishop, Brian L.; Duncan, Matthew
                         J.; Krishnan, K. Ranga Rama; Song, Jeongmin; Li,
                         Guojie; Zaas, David W.
PATENT ASSIGNEE(S):      Duke University, USA
SOURCE:                  PCT Int. Appl., 121pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2008157205         A2    20081224    WO 2008-US66647         20080612
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
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PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2007-944182P P 20070615

OTHER SOURCE(S): MARPAT 150:71089

AB Methods and compns. are provided for treating a urinary tract infection (UTI). The methods involve administering to a subject in need thereof a cAMP elevator or agent that mimics cAMP, particularly a labdane diterpene such as forskolin or a derivative or analog thereof in a therapeutically effective amount to treat a UTI. The methods may further include administration of at least one cAMP elevator in combination with one or more addnl. active compds. from other classes of therapeutic agents, such as antimicrobial agents or cholesterol-lowering drugs. Compns. of the invention include pharmaceutical compns. and kits for treating a UTI in a subject in need thereof that include therapeutically effective amts. of at least two cAMP elevators, particularly where one of the cAMP elevators is a labdane diterpene such as forskolin or a derivative or analog thereof. In particular, the compns. and kits may also include at least one cAMP elevator in combination with one or more addnl. active compds. from other classes of therapeutic agents, such as antimicrobial agents or cholesterol-lowering drugs.

L4 ANSWER 3 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:1303922 CAPLUS

DOCUMENT NUMBER: 149:525455

TITLE: Modulation of blood brain barrier protein expression

PATENT ASSIGNEE(S): St. Louis University, USA

SOURCE: PCT Int. Appl., 125pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008131431	A2	20081030	WO 2008-US61316	20080423

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2007-925820P P 20070423

AB There are disclosed agents that inhibit blood brain barrier proteins (BBBP). Such agents are useful in controlling agents entering and exiting the CNS. This allows for drugs to be more effective and/or allowing side effects of the drugs to be lowered. Administration of antisense oligonucleotides targeting β-F1 ATPase along with pituitary adenylate cyclase-activating polypeptide 27 significantly improved learning in a mouse model of Alzheimer's disease.

L4 ANSWER 4 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1065739 CAPLUS
DOCUMENT NUMBER: 149:486137
TITLE: Disruption of LH-induced testosterone biosynthesis in testicular Leydig cells by triclosan: Probable mechanism of action
AUTHOR(S): Kumar, Vikas; Balomajumder, Chandrajeet; Roy, Partha
CORPORATE SOURCE: Molecular Endocrinology Laboratory, Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, 247667, India
SOURCE: Toxicology (2008), 250(2-3), 124-131
CODEN: TXCYAC; ISSN: 0300-483X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Triclosan (TCS) is an antimicrobial chemical widely used in different com. prepns. The present study demonstrated the mechanism of action of TCS-induced anti-androgenecity in rat Leydig cells. Treatment of purified cells with increasing concns. of TCS (0.001, 0.01, 0.1, 1 and 10 μM) resulted in a significantly decreased activity of adenylyl cyclase enzyme which was followed by a decreased synthesis of cAMP. This decreased cAMP level resulted in the disruption of entire steroidogenic cascade causing a depressed synthesis of testosterone. However, TCS-induced decrease in the production of testosterone returned to normalcy when cells were treated with forskolin (an adenylyl cyclase activator). Transcription followed by translation of four prominent steroidogenic enzyme/proteins, cytochrome P 450 side chain cleavage (P450scc), 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD) and steroidogenic acute regulatory (StAR) protein, also decreased in a dose-dependent manner in TCS-treated Leydig cells as determined by RT-PCR, enzyme assay and Western blot. These results suggested that the disruption of the activity of adenylyl cyclase enzyme by TCS in turn leads to the disruption of intermediate steroidogenic cascade causing a depressed testosterone production The study further confirmed the anti-androgenic activity of TCS in Leydig cells with highest effective concentration at 1 μM.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:712829 CAPLUS
DOCUMENT NUMBER: 149:170919
TITLE: The cyclic AMP-dependent catabolite repression system of Serratia marcescens mediates biofilm formation through regulation of type 1 fimbriae
AUTHOR(S): Kalivoda, Eric J.; Stella, Nicholas A.; O'Dee, Dawn M.; Nau, Gerard J.; Shanks, Robert M. Q.
CORPORATE SOURCE: Charles T. Campbell Laboratory of Ophthalmic Microbiology, Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, PA, 15213, USA
SOURCE: Applied and Environmental Microbiology (2008), 74(11), 3461-3470
CODEN: AEMIDF; ISSN: 0099-2240
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanisms by which environmental carbon sources regulate biofilm formation are poorly understood. This study investigates the roles of glucose and the catabolite repression system in Serratia marcescens biofilm formation. The abilities of this opportunistic pathogen to

proliferate in a wide range of environments, to cause disease, and to resist antimicrobials are linked to its ability to form biofilms. We observed that growth of S. marcescens in glucose-rich medium strongly stimulated biofilm formation, which contrasts with previous studies showing that biofilm formation is inhibited by glucose in Escherichia coli and other enteric bacteria. Glucose uptake is known to inversely mediate intracellular cAMP (cAMP) synthesis through regulation of adenylate cyclase (cyaA) activity, which in turn controls fundamental processes such as motility, carbon utilization and storage, pathogenesis, and cell division in many bacteria. Here, we demonstrate that mutation of catabolite repression genes that regulate cAMP levels (crr and cyaA) or the ability to respond to cAMP (crp) confers a large increase in biofilm formation. Suppressor anal. revealed that phenotypes of a cAMP receptor protein (crp) mutant require the fimABCD operon, which is responsible for type 1 fimbria production Consistently, fimA transcription and fimbria production were determined to be upregulated in a cyaA mutant background by using quant. real-time reverse transcription-PCR and transmission electron microscopy anal. The regulatory pathway by which environmental carbon sources influence cAMP concns. to alter production of type 1 fimbrial adhesins establishes a novel mechanism by which bacteria control biofilm development.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:632821 CAPLUS
DOCUMENT NUMBER: 148:580339
TITLE: Antifungal mechanism of hinokitiol against Candida albicans
AUTHOR(S): Komaki, Nami; Watanabe, Toshihiko; Ogasawara, Ayako; Sato, Norifumi; Mikami, Takeshi; Matsumoto, Tatsuji
CORPORATE SOURCE: Department of Microbiology, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, 981-8558, Japan
SOURCE: Biological & Pharmaceutical Bulletin (2008), 31(4), 735-737
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The growth of Candida albicans was dose-dependently inhibited by addition of hinokitiol. The sensitivity of C. albicans to hinokitiol under aerobic conditions was higher than that under anaerobic conditions. Amount of ATP in C. albicans was not inhibited by hinokitiol under both conditions. The expression of mRNAs related to the growth signal, CYR1 and RAS1, was inhibited by hinokitiol. These findings suggested that the growth inhibition of C. albicans by hinokitiol was due to the interruption of RAS-signal transmission, such as the cAMP pathway.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:588852 CAPLUS
DOCUMENT NUMBER: 148:536017
TITLE: Attenuated bacteria expressing recombinant antigens and protein toxins and their use in tumor vaccines and immunotherapy
INVENTOR(S): Fensterle, Joachim; Gentschev, Ivaylo; Rapp, Ulf R.; Goebel, Werner
PATENT ASSIGNEE(S): Aeterna Zentaris G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 86pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1921149	A1	20080514	EP 2006-123974	20061113
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
WO 2008058944	A1	20080522	WO 2007-EP62237	20071113
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.:			
EP 2006-123974	A	20061113
US 2006-865484P	P	20061113
US 2007-939140P	P	20070521

AB The invention relates to a microorganism as a carrier of nucleotide sequences coding for antigens and protein toxins comprising the following components: (I) at least one nucleotide sequence coding for at least one complete or partial antigen of at least one wild-type or mutated protein; and (II) at least one nucleotide sequence coding for at least one protein toxin and/or at least one protein toxin subunit; and (III) (a) at least one nucleotide sequence coding for at least one transport system which enables the expression of the expression products of component (I) and component (II) on the outer surface of the microorganism and/or enables the secretion of the expression products of component (I) and component (II); and/or (III) (b) optionally, at least one nucleotide sequence coding for at least one protein for lysing the microorganism in the cytosol of mammalian cells and for intracellularly releasing plasmids or expression vectors, which are contained in the lysed microorganism; and (IV) at least one nucleotide sequence for at least one activation sequence for the expression of one or more of components (I) to (III), wherein said activation sequence can be activated in the microorganism and/or is tissue cell-specific, tumor cell-specific, macrophage-specific, dendrite-specific, lymphocyte-specific, function-specific or "non-cell-specific"; wherein any of components (I) to (IV) can be present either once or several times and either identical or different. The invention also discloses a process of manufacturing thereof, corresponding plasmids or expression vectors and uses of the microorganism as a medicament. The invention specifically claims use of chimeric proteins cholera toxin subunit B (CtxB)-prostate specific antigen (PSA), CtxB-B-Raf kinase domain, CtxB-B-Raf kinase domain mutants, CtxB-hemagglutinin HA1, and CtxB-hemagglutinin HA12C. The chimeric proteins are expressed under control of an endogenous promoter of the Escherichia coli hly locus and also contain signal sequences from the Hly secretion system. Mice were immunized intragastrically with bacteria expressing a CtxB-PSA chimeric protein and an immune response was observed comprising CD8+ T cells and the innate immune system (probably NK cells). The immunized mice showed reduced tumor volume at 9, 12, and 14 days after tumor challenge by s.c. injection of P815 cell line expressing full-length prostate specific antigen.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:131168 CAPLUS
DOCUMENT NUMBER: 148:158659
TITLE: Diterpenes: a therapeutic promise for cardiovascular diseases
AUTHOR(S): Tirapelli, Carlos R.; Ambrosio, Sergio R.; da Costa, Fernando B.; de Oliveira, Ana M.
CORPORATE SOURCE: Departamento de Enfermagem Psiquiatrica e Ciencias Humanas, Escola de Enfermagem de Ribeirao Preto, USP, Ribeirao Preto, Brazil
SOURCE: Recent Patents on Cardiovascular Drug Discovery (2008), 3(1), 1-8
CODEN: RPCDFC; ISSN: 1574-8901
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The research, development and use of natural products as therapeutic agents, especially those derived from plants, have been increasing in recent years. There has been great deal of focus on the naturally occurring antispasmodic phytochems. as potential therapy for cardiovascular diseases. Naturally occurring diterpenes exert several biol. activities such as anti-inflammatory action, antimicrobial and antispasmodic activities. Several diterpenes have been shown to have pronounced cardiovascular effects, for example, grayanotoxin I produces pos. inotropic responses, forskolin is a well-known activator of adenylate cyclase, eleganolone and 14-deoxyandrographolide exhibit vasorelaxant properties and marrubenol inhibits smooth muscle contraction by blocking L-type calcium channels. In the last few years, we have investigated the biol. activity of kaurane and pimarane-type diterpenes, which are the main secondary metabolites isolated from the roots of Viguiera robusta and V. arenaria, resp. These diterpenoids exhibit vasorelaxant action and inhibit the vascular contractility mainly by blocking extracellular Ca2+ influx. Moreover, kaurane and pimarane-type diterpenes decreased mean arterial blood pressure in normotensive rats. Diterpenes likely fulfil the definition of a pharmacol. preconditioning class of compds. and give hope for the therapeutic use in cardiovascular diseases. This article will review patents, structure-activity relationship, pharmacol., antihypertensive efficiency, and the vascular mechanisms underlying the effects of diterpenes. Careful examination of the cardiovascular effects exhibited by kaurane and pimarane-type diterpenes will be provided.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1212472 CAPLUS
DOCUMENT NUMBER: 147:463069
TITLE: Protein and cDNA sequence sequences of human and mouse G-protein coupled receptor GPR86 and screening for agonist or antagonist of GPR86
INVENTOR(S): Brice, Nicola; Carlton, Mark; Dixon, John; Hendrick, Alan; Malinge, Isabelle; Messager, Sophie; Zahn, Dirk
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 66pp., Cont.-in-part of Appl. No. PCT/GB05/002601.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070248545	A1	20071025	US 2006-644011	20061221
WO 2006003422	A1	20060112	WO 2005-GB2601	20050701

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.:	GB 2004-14798	A	20040701
	US 2004-586513P	P	20040709
	GB 2005-10253	A	20050519
	US 2005-683471P	P	20050520
	WO 2005-GB2601	A2	20050701

AB Describe a method of identifying a mol. suitable for the treatment, prophylaxis or alleviation of a GPR86 associated disease, in particular inflammatory disease or pain. The method comprises determining whether a candidate mol. is an agonist or antagonist of GPR86 polypeptide. Also provided are the protein and cDNA sequence sequences of human and mouse G-protein coupled receptor GPR86. Transgenic GPR86 knock-out mice were produced and tested for sensitivity to exterminal stimuli and pain (analgesis testing).

L4 ANSWER 10 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2007:1111492 CAPLUS
DOCUMENT NUMBER:	147:404626
TITLE:	Specific Leukotriene Receptors Couple to Distinct G Proteins to Effect Stimulation of Alveolar Macrophage Host Defense Functions
AUTHOR(S):	Peres, Camila M.; Aronoff, David M.; Serezani, Carlos H.; Flamand, Nicolas; Faccioli, Lucia H.; Peters-Golden, Marc
CORPORATE SOURCE:	Division of Pulmonary and Critical Care Medicine, Univ. Michigan Health Syst., Ann Arbor, MI, 48109, USA
SOURCE:	Journal of Immunology (2007), 179(8), 5454-5461 CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER:	American Association of Immunologists
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Leukotrienes (LTs) are lipid mediators implicated in asthma and other inflammatory diseases. LTB4 and LTD4 also participate in antimicrobial defense by stimulating phagocyte functions via ligation of B leukotriene type 1 (BLT1) receptor and cysteinyl LT type 1 (cysLT1) receptor, resp. Although both Gαi and Gαq proteins have been shown to be coupled to both BLT1 and cysLT1 receptors in transfected cell systems, there is little known about specific G protein subunit coupling to LT receptors, or to other G protein–coupled receptors, in primary cells. Here, the authors sought to define the role of specific G proteins in pulmonary alveolar macrophage (AM) innate immune responses to LTB4 and LTD4. LTB4 but not LTD4 reduced cAMP levels in rat AM by a pertussis toxin (PTX)–sensitive mechanism. Enhancement of FcγR–mediated phagocytosis and bacterial killing by LTB4 was also PTX-sensitive, whereas that induced by LTD4 was not. LTD4 and LTB4

induced Ca2+ and intracellular inositol monophosphate accumulation, resp., highlighting the role of Gαq protein in mediating PTX-insensitive LTD4 enhancement of phagocytosis and microbicidal activity. Studies with liposome-delivered G protein blocking Abs indicated a dependency on specific Gαq/11 and Gαi3 subunits, but not Gαi2 or Gβγ, in LTB4-enhanced phagocytosis. The selective importance of Gαq/11 protein was also demonstrated in LTD4-enhanced phagocytosis. The present investigation thus identifies differences in specific G protein subunit coupling to LT receptors in antimicrobial responses and highlights the importance of defining the specific G proteins coupled to heptahelical receptors in primary cells, rather than simply using heterologous expression systems.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:1064219 CAPLUS

DOCUMENT NUMBER: 147:383999

TITLE: Detection of gene expression by specific cell types in mixed samples or tissues such as mouse thymus cortex or medullary stromal cells using DGEM (differential gene expression mapping)

INVENTOR(S): Petrie, Howard T.

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 257pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007106507	A2	20070920	WO 2007-US6363	20070314
WO 2007106507	A3	20090205		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: US 2006-782124P P 20060314

AB Differential gene expression mapping (DGEM) utilizes (1) laser capture microdissection or other methods of microdissection of the tissue regions of interest; (2) microarray screening of RNA isolated from the microdissected regions and anal. of purified individual cellular components from the tissue; and (3) computational profiling or subtraction to identify gene expression by specific cell types in situ. The method was applied to stromal cells from whole cortical and medullary regions of C57BL6 mouse thymus. As a result, DGEM, a reverse identification approach, solves previously insurmountable problems, as the lymphoid progenitors can be readily isolated, allowing fluctuations in receptor expression on lymphoid cells to be used to predict stratified stromal signals. An algorithmic approach can be used for calculating the expression profile of a tissue/sample of interest that consists of at least two types of cells. Specifically, the approach electronically subtracts the

expression profile of one component of a sample from the expression profile of the total sample, thus revealing the profiles of the other component. To confirm the robustness of the DGEM procedure, the gene expression profiles from each sample of whole medulla, whole cortex, cortical thymocytes and medullary thymocytes was sorted based only on the expression data.

L4 ANSWER 12 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1338305 CAPLUS
DOCUMENT NUMBER: 146:87576
TITLE: Pharmaceutical compositions comprising antiscarring agents
INVENTOR(S): Hunter, William L.; Toleikis, Philip M.; Gravett, David M.; Maiti, Arpita; Liggins, Richard T.; Takacs-Cox, Aniko; Avelar, Rui; Signore, Pierre E.; Loss, Troy A. E.; Hutchinson, Anne; McDonald-Jones, Gaye; Lakhani, Fara
PATENT ASSIGNEE(S): Angiotech International A.-G., Switz.
SOURCE: PCT Int. Appl., 4712pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006135479	A2	20061221	WO 2006-US13030	20060331
WO 2006135479	A3	20070412		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
WO 2006121522	A2	20061116	WO 2006-US11726	20060331
WO 2006121522	A3	20080502		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AP, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, EA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, EP, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, OA, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 2005-679293P	P	20050510
US 2005-679291P	P	20050510

AB The present invention provides devices or implants that comprise anti-scarring agents, methods or making such devices or implants, and methods of inhibiting fibrosis between the devices or implants and tissue surrounding the devices or implants. The present invention also provides compns. that comprise anti-fibrotic agents, and their uses

in various medical applications including the prevention of surgical adhesions, treatment of inflammatory arthritis, treatment of scars and keloids, the treatment of vascular disease, and the prevention of cartilage loss. MPEG and MePEG2000-PDLLA are combined and heated to 75°. After the polymers are completely melted and mixed, the temperature was decreased to 55°. A juglone solution in THF is prepared and is poured into the polymer solution under constant stirring. The juglone containing micelles are dried and the resultant solid material is ground on a 2 mm mesh screen after cooling.

L4 ANSWER 13 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:137386 CAPLUS
DOCUMENT NUMBER: 145:137046
TITLE: Exploiting common targets in human fertilization and HIV infection: development of novel contraceptive microbicides
AUTHOR(S): Doncel, Gustavo F.
CORPORATE SOURCE: CONRAD, Department of Obstetrics and Gynecology, The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
SOURCE: Human Reproduction Update (2006), 12(2), 103-117
CODEN: HRUPF8; ISSN: 1355-4786
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The continued high rates of unintended pregnancies and the unrelentless expansion of the acquired immune deficiency syndrome (AIDS) epidemic, especially in less developed countries, warrant the development of novel strategies to help individuals avoid these risks. Dually active compds. displaying contraceptive and microbicidal anti-human immunodeficiency virus (anti-HIV) properties constitute one such strategy. Sharing the same anatomical and functional context, sperm fertilization and genital infection by HIV offer an opportunity for simultaneous intervention. Some of the mols. and mechanisms used by sperm to fertilize the oocyte are similar, if not identical, to those used by HIV while infecting host cells. An example of common structures is the lipid membrane surrounding the spermatozoon and the HIV core. Disruption of its architecture by surface-active compds. exerts both spermicidal and virucidal activity. A more specific alteration of lipid rafts [membrane microdomains enriched in cholesterol and glycosylphosphatidylinositol (GPI)-anchored proteins] by β-cyclodextrins also results in similar effects. During fertilization and infection, both sperm and HIV interact with their target cell receptors through chemical charges, hydrophobic forces and carbohydrate recognition. Anionic polymers such as cellulose sulfate and polystyrene sulfonate (PSS) inhibit sperm and HIV cell binding. Because some of the mols. involved in this interaction, e.g. heparin sulfate proteoglycan, are also used by other pathogens to infect their target tissues, polyanions exert broad antimicrobial activity as well. During fertilization and infection, sperm and HIV, as well as other microbes, use signal transduction mols. and mechanisms such as adenyl cyclase/cyclic adenosine monophosphate (cAMP)-dependent kinase, calcium and tyrosine phosphorylation, whose inhibition has been shown to impair sperm function and HIV replication. These commonalities at the level of sperm and HIV structure, cell binding and fusion processes, and signaling pathways therefore provide the biol. framework to develop bifunctional inhibitors with both antimicrobial and contraceptive properties.
REFERENCE COUNT: 224 THERE ARE 224 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:120414 CAPLUS
DOCUMENT NUMBER: 144:184702
TITLE: Gene expression profiles for identifying patients at risk of developing encephalitis following immunotherapy for Alzheimer's disease
INVENTOR(S): O'Toole, Margot; Dorner, Andrew J.; Janszen, Derek B.; Slonim, Donna K.; Mounts, William M.; Reddy, Padmalatha S.; Hill, Andrew A.
PATENT ASSIGNEE(S): Wyeth, USA
SOURCE: PCT Int. Appl., 298 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006014755	A2	20060209	WO 2005-US25771	20050720
WO 2006014755	A3	20060413		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2571856	A1	20060209	CA 2005-2571856	20050720
US 20060073496	A1	20060406	US 2005-186236	20050720
EP 1784509	A2	20070516	EP 2005-795582	20050720
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.:
US 2004-589877P P 20040720
US 2005-672716P P 20050418
WO 2005-US25771 W 20050720

AB The present invention generally relates to a method for an improved treatment for Alzheimer's disease (AD) using immunotherapy, e.g., immunotherapy targeting β amyloid (Aβ) and immunotherapy based on AN1792. By ANOVA and GeneCluster analyses of Affymetrix U133A GeneChip data, statistically significant assocns. were detected between the gene expression profiles of peripheral blood mononuclear cells of patients prior to immunization with AN1792 and the post-immunization development of encephalitis. In addition, statistically significant assocns. were found between the pre-immunization gene expression profile in PBMCs and post-immunization development of IgG response. The method allows for predicting an adverse clin. response, and therefore allows for an improved safety profile of AN1792. In another embodiment, the method allows for predicting a favorable clin. response, and therefore allows for an improved efficacy profile of AN1792. The methods of the present invention may be combined to predict a favorable clin. response and the lack of an adverse clin. response.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:107205 CAPLUS

DOCUMENT NUMBER: 144:308078
TITLE: Ras pathway signaling accelerates programmed cell death in the pathogenic fungus Candida albicans
AUTHOR(S): Phillips, Andrew J.; Crowe, Jonathan D.; Ramsdale, Mark
CORPORATE SOURCE: Aberdeen Fungal Group, Institute of Medical Sciences, University of Aberdeen, Foresterhill, AB25 2ZD, UK
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2006), 103(3), 726-731
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A better understanding of the mol. basis of programmed cell death (PCD) in fungi could provide information that is useful in the design of antifungal drugs that combat life-threatening fungal infections. Harsh environmental stresses, such as acetic acid or hydrogen peroxide, have been shown to induce PCD in the pathogenic fungus Candida albicans. In this study, we show that dying cells progress from an apoptotic state to a secondary necrotic state and that the rate at which this change occurs is proportional to the intensity of the stimulus. Also, we found that the temporal response is modulated by Ras-cAMP-PKA signals. Mutations that block Ras-cAMP-PKA signaling (ras1Δ, cdc35Δ, tpk1Δ, and tpk2Δ) suppress or delay the apoptotic response, whereas mutations that stimulate signaling (RAS1val13 and pde2Δ) accelerate the rate of entry of cells into apoptosis. Pharmacol. stimulation or inhibition of Ras signaling reinforces these findings. Transient increases in endogenous cAMP occur under conditions that stimulate apoptosis but not growth arrest. Death-specific changes in the abundance of different isoforms of the PKA regulatory subunit, Bcy1p, are also observed Activation of Ras signals may regulate PCD of C. albicans, either by inhibiting antiapoptotic functions (such as stress responses) or by activating proapoptotic functions.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:714054 CAPLUS
DOCUMENT NUMBER: 143:171291
TITLE: Calcium-sensing soluble adenylyl cyclase mediates TNF signal transduction in human neutrophils
AUTHOR(S): Han, Hyunsil; Stessin, Alexander; Roberts, Julia; Hess, Kenneth; Gautam, Narinder; Kamenetsky, Margarita; Lou, Olivia; Hyde, Edward; Nathan, Noah; Muller, William A.; Buck, Jochen; Levin, Lonny R.; Nathan, Carl
CORPORATE SOURCE: Department of Microbiology and Immunology, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of Experimental Medicine (2005), 202(3), 353-361
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Through chemical screening, we identified a pyrazolone that reversibly blocked the activation of phagocyte oxidase (phox) in human neutrophils in response to tumor necrosis factor (TNF) or formylated peptide. The pyrazolone spared activation of phox by phorbol ester or bacteria, bacterial killing, TNF-induced granule exocytosis and phox assembly, and endothelial transmigration. We traced the pyrazolone's mechanism of action to inhibition of TNF-induced intracellular Ca2+

elevations, and identified a nontransmembrane ("soluble") adenylyl cyclase (sAC) in neutrophils as a Ca2+-sensing source of cAMP. A sAC inhibitor mimicked the pyrazolone's effect on phox. Both compds. blocked TNF-induced activation of Rap1A, a phox-associated guanosine triphosphatase that is regulated by cAMP. Thus, TNF turns on phox through a Ca2+-triggered, sAC-dependent process that may involve activation of Rap1A. This pathway may offer opportunities to suppress oxidative damage during inflammation without blocking antimicrobial function.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:395039 CAPLUS

DOCUMENT NUMBER: 142:451805

TITLE: Macromer-melt formulations for sustained-release delivery of drug and biologically active substance

INVENTOR(S): Rowe, Stephen C.; Ananvajjula, Durga

PATENT ASSIGNEE(S): Azopax Therapeutics LLC, USA

SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005039502	A2	20050506	WO 2004-US35346	20041022
WO 2005039502	A3	20050728		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2585024	A1	20050506	CA 2004-2585024	20041022
US 20070053954	A1	20070308	US 2006-410269	20060424

PRIORITY APPLN. INFO.:

US 2003-514286P	P	20031024
US 2003-514243P	P	20031024
US 2003-514292P	P	20031024
WO 2004-US35267	A2	20041022
WO 2004-US35346	W	20041022
WO 2004-US35088	A2	20041025

AB The invention provides methods and articles for the administration of a biol. active substance (BAS). The articles made using the method of the invention have increased percentages (weight/weight) of macromer, increased crosslinking d., and reduced pore size in comparison to articles made using solution methods. The articles exhibit extended release profiles, even for low mol. weight active substances. These methods and articles provide for the controlled and sustained delivery of relatively large quantities of these substances with a low burst effect. The invention also features methods of treating a mammal using the articles described herein.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:248644 CAPLUS

DOCUMENT NUMBER: 142:274057
TITLE: Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy
INVENTOR(S): Liew, Choong-chin
PATENT ASSIGNEE(S): Chondrogene Limited, Can.
SOURCE: U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 47
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040241727	A1	20041202	US 2004-812731	20040330
US 20040014059	A1	20040122	US 2002-268730	20021009
US 20050191637	A1	20050901	US 2004-803737	20040318
US 20050196762	A1	20050908	US 2004-803759	20040318
US 20050196763	A1	20050908	US 2004-803857	20040318
US 20050196764	A1	20050908	US 2004-803858	20040318
US 20050208505	A1	20050922	US 2004-803648	20040318
US 20040241727	A1	20041202	US 2004-812731	20040330

PRIORITY APPLN. INFO.:

US 1999-115125P	P	19990106
US 2000-477148	B1	20000104
US 2002-268730	A2	20021009
US 2003-601518	A2	20030620
US 2004-802875	A2	20040312
US 2004-812731	A	20040330

AB The present invention is directed to detection and measurement of gene transcripts and their equivalent nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstract record is one of 3 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L4 ANSWER 19 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:627698 CAPLUS
DOCUMENT NUMBER: 141:223950
TITLE: Temporin A and Related Frog Antimicrobial Peptides Use Formyl Peptide Receptor-Like 1 as a Receptor to Chemoattract Phagocytes
AUTHOR(S): Chen, Qian; Wade, David; Kurosaka, Kahori; Wang, Zhao Yuan; Oppenheim, Joost J.; Yang, De
CORPORATE SOURCE: Laboratory of Molecular Immunoregulation, Center for Cancer Research, National Inst. of Health, Frederick, MD, 21702-1201, USA
SOURCE: Journal of Immunology (2004), 173(4), 2652-2659
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Many mammalian antimicrobial peptides (AMPs) have multiple effects on antimicrobial immunity. The authors found that temporin A (TA), a representative frog-derived AMP, induced the migration of human monocytes, neutrophils, and macrophages with a bell-shaped response curve in a pertussis toxin-sensitive manner, activated p44/42

MAPK, and stimulated Ca2+ flux in monocytes, suggesting that TA is capable of chemoattracting phagocytic leukocytes by the use of a Giα protein-coupled receptor. TA-induced Ca2+ flux in monocytes was cross-desensitized by an agonistic ligand MMK-1 specific for formyl peptide receptor-like 1 (FPRL1) and vice versa, suggesting that TA uses FPRL1 as a receptor. This conclusion was confirmed by data showing that TA selectively stimulated chemotaxis of HEK 293 cells transfected with human FPRL1 or its mouse ortholog, murine formyl peptide receptor 2. In addition, TA elicited the infiltration of neutrophils and monocytes into the injection site of mice, indicating that TA is also functionally chemotactic in vivo. Examination of two addnl. temporins revealed that Rana-6 was also able to attract human phagocytes using FPRL1, but temporin 1P selectively induced the migration of neutrophils using a distinct receptor. Comparison of the chemotactic and antimicrobial activities of several synthetic analogs suggested that these activities are likely to rely on different structural characteristics. Overall, the results demonstrate that certain frog-derived temporins have the capacity to chemoattract phagocytes by the use of human FPRL1 (or its orthologs in other species), providing the first evidence suggesting the potential participation of certain amphibian antimicrobial peptides in host antimicrobial immunity.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:502177 CAPLUS

DOCUMENT NUMBER: 141:100310

TITLE: Prostaglandin E2 Inhibits Alveolar Macrophage Phagocytosis through an E-Prostanoid 2 Receptor-Mediated Increase in Intracellular Cyclic AMP

AUTHOR(S): Aronoff, David M.; Canetti, Claudio; Peters-Golden, Marc

CORPORATE SOURCE: Divisions of Infectious Diseases and Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI, 48109-0642, USA

SOURCE: Journal of Immunology (2004), 173(1), 559-565 CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Prostaglandin E2 is a potent lipid mediator of inflammation that effects changes in cell functions through ligation of four distinct G protein-coupled receptors (E-prostanoid (EP)1, EP2, EP3, and EP4). During pneumonia, PGE2 production is enhanced. In the present study, we sought to assess the effect of endogenously produced and exogenously added PGE2 on FcRγ-mediated phagocytosis of bacterial pathogens by alveolar macrophages (AMs), which are critical participants in lung innate immunity. We also sought to characterize the EP receptor signaling pathways responsible for these effects. PGE2 (1-1000 nM) dose-dependently suppressed the phagocytosis by rat AMs of IgG-opsonized erythrocytes, immune serum-opsonized Klebsiella pneumoniae, and IgG-opsonized Escherichia coli. Conversely, phagocytosis was stimulated by pretreatment with the cyclooxygenase inhibitor indomethacin. PGE2 suppression of phagocytosis was associated with enhanced intracellular cAMP production Expts. using both forskolin (adenylate cyclase activator) and rolipram (phosphodiesterase IV inhibitor) confirmed the inhibitory effect of cAMP stimulation. Immunoblot anal. of rat AMs identified expression of only EP2 and EP3 receptors. The selective EP2 agonist butaprost, but neither the EP1/EP3 agonist sulprostone nor the EP4-selective agonist ONO-AE1-329, mimicked the effects of PGE2 on phagocytosis and cAMP stimulation. Addnl., the EP2

antagonist AH-6809 abrogated the inhibitory effects of both PGE2 and butaprost. We confirmed the specificity of our results by showing that AMs from EP2-deficient mice were resistant to the inhibitory effects of PGE2. Our data support a neg. regulatory role for PGE2 on the antimicrobial activity of AMs, which has important implications for future efforts to prevent and treat bacterial pneumonia.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:502135 CAPLUS
DOCUMENT NUMBER: 141:122289
TITLE: Identification of Neutrophil Granule Protein Cathepsin G as a Novel Chemotactic Agonist for the G Protein-Coupled Formyl Peptide Receptor
AUTHOR(S): Sun, Ronghua; Iribarren, Pablo; Zhang, Ning; Zhou, Ye; Gong, Wanghua; Cho, Edward H.; Lockett, Stephen; Chertov, Oleg; Bednar, Filip; Rogers, Thomas J.; Oppenheim, Joost J.; Wang, Ji Ming
CORPORATE SOURCE: Laboratory of Molecular Immunoregulation, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, MD, 21702, USA
SOURCE: Journal of Immunology (2004), 173(1), 428-436
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antimicrobial and proinflammatory neutrophil granule protein cathepsin G (CaG) has been reported as a chemoattractant for human phagocytic leukocytes by using a putative G protein coupled receptor. In an effort to identify potential CaG receptor(s), the authors found that CaG-induced phagocyte migration was specifically attenuated by the bacterial chemotactic peptide fMLP, suggesting these 2 chemoattractants might share a receptor. In fact, CaG chemoattracts rat basophilic leukemia cells (RBL cells) expressing the high affinity human fMLP receptor FPR, but not parental RBL cells or cells transfected with other chemoattractant receptors. In addition, a specific FPR Ab and a defined FPR antagonist, cyclosporin H, abolished the chemotactic response of phagocytes and FPR-transfected cells to CaG. Furthermore, CaG down-regulated the cell surface expression of FPR in association with receptor internalization. Unlike fMLP, CaG did not induce potent Ca2+ flux and was a relatively weaker activator of MAPKs via FPR. Yet CaG activated an atypical protein kinase C isoenzyme, protein kinase Cζ, which was essential for FPR to mediate the chemotactic activity of CaG. The authors' studies thus identify CaG as a novel, host-derived chemotactic agonist for FPR and expand the functional scope of this receptor in inflammatory and immune responses.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:355085 CAPLUS
DOCUMENT NUMBER: 140:369944
TITLE: Human tissue-specific housekeeping genes identified by expression profiling
INVENTOR(S): Aburatani, Hiroyuki; Yamamoto, Shogo
PATENT ASSIGNEE(S): NGK Insulators, Ltd., Japan
SOURCE: PCT Int. Appl., 372 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035785	A1	20040429	WO 2002-JP10753	20021016
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002344094	A1	20040504	AU 2002-344094	20021016
US 20040229233	A1	20041118	US 2003-684422	20031015
PRIORITY APPLN. INFO.:			US 2002-418614P P	20021016
			WO 2002-JP10753 A	20021016

AB Housekeeping genes commonly expressed in 35 different human tissues, oligonucleotide probes and DNA microarrays containing them, are disclosed.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:781545 CAPLUS

DOCUMENT NUMBER: 140:25362

TITLE: Cyclic AMP signaling pathway modulates susceptibility of Candida species and Saccharomyces cerevisiae to antifungal azoles and other sterol biosynthesis inhibitors

AUTHOR(S): Jain, Pooja; Akula, Indira; Edlind, Thomas

CORPORATE SOURCE: Department of Microbiology & Immunology, Drexel University College of Medicine, Philadelphia, PA, 19129, USA

SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(10), 3195-3201
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Azoles are widely used antifungals; however, their efficacy is compromised by fungistatic activity and selection of resistant strains during treatment. Recent studies demonstrated roles for the protein kinase C and Ca signaling pathways in modulating azole activity. Here we explored a role for the signaling pathway mediated by cAMP, which is synthesized by the regulated action of adenylate cyclase (encoded by CDC35 in Candida albicans and CYR1 in Saccharomyces cerevisiae) and cyclase-associated protein (encoded by CAP1 and SRV2, resp.). Relative to wild-type strains, C. albicans and S. cerevisiae strains mutated in these genes were hypersusceptible to fluconazole (>4- to >16-fold-decreased 48-h MIC), itraconazole (>8- to >64-fold), or miconazole (16- to >64-fold). Similarly, they were hypersusceptible to terbinafine and fenpropimorph (2- to >16-fold), which, like azoles, inhibit sterol biosynthesis. Addition of cAMP to the medium at least partially reversed the hypersusceptibility of Ca-cdc35 and Sc-cry1-2 mutants. An inhibitor of mammalian adenylate cyclase, MDL-12330A, was tested in combination with azoles; a synergistic effect was observed against azole-susceptible and -resistant strains of C. albicans and 5 of 6 non-C. albicans Candida species. Anal. of cAMP levels after glucose induction in the presence and absence of MDL-12330A confirmed that it acts by inhibiting cAMP synthesis

in yeast. RNA anal. suggested that a defect in azole-dependent upregulation of the multidrug transporter gene CDR1 contributes to the hypersusceptibility of the Ca-cdc35 mutant. Our results implicate cAMP signaling in the yeast azole response; compds. similar to MDL-12330A may be useful adjuvants in azole therapy.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:218830 CAPLUS
DOCUMENT NUMBER: 139:111113
TITLE: Small ligands modulating the activity of mammalian adenylyl cyclases: A novel mode of inhibition by calmidazolium
AUTHOR(S): Haunso, Anders; Simpson, James; Antoni, Ferenc A.
CORPORATE SOURCE: Department of Neuroscience, University of Edinburgh, Edinburgh, UK
SOURCE: Molecular Pharmacology (2003), 63(3), 624-631
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mol. cloning of membrane-spanning mammalian adenylyl cyclases (ACs) has led to the discovery of nine different isotypes, making ACs potentially useful therapeutic targets. This study investigated the mechanism by which fungicidal nitroimidazole compds. modulate AC activity. Current evidence indicates that biol. control of AC activity occurs through the cytosolic domains. Hence, full-length ACII, ACIX, and recombinant fusion proteins composed of the cytoplasmic loops of human ACIX or the first and second cytoplasmic loops of rat ACV and ACII, resp., were expressed in human embryonic kidney 293 cells. The AC activities of the resp. proteins were characterized, and their modulation by nitroimidazoles was investigated. Calmidazolium inhibited the activities of both full-length ACs and soluble fusion proteins (IC50, .apprx.10 μM). Inhibition of ACIX by calmidazolium was mediated by direct interaction with the catalytic core in a noncompetitive fashion. ACIX was essentially insensitive to 2'-deoxyadenosine 3'-monophosphate, a known blocker of AC activity. The ACV-ACII fusion protein was inhibited by calmidazolium (IC50, .apprx.20 μM) as well as by 2'-deoxyadenosine 3'-AMP (IC50, .apprx.2 μM), in a manner indicating independent mechanisms of action. Taken together, the data demonstrate that ACIX is insensitive to adenosine analogs and that calmidazolium inhibits AC activity by a novel, noncompetitive mechanism.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:695728 CAPLUS
DOCUMENT NUMBER: 137:210997
TITLE: Compounds and methods for the treatment of urogenital disorders
INVENTOR(S): Mak, Vivien H. W.; Grayson, Stephen
PATENT ASSIGNEE(S): Cellegy Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069906	A2	20020912	WO 2002-US7026	20020306
WO 2002069906	A3	20031120		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2440141	A1	20020912	CA 2002-2440141	20020306
AU 2002254142	A1	20020919	AU 2002-254142	20020306
US 20020198136	A1	20021226	US 2002-94409	20020306
US 6987129	B2	20060117		
EP 1383502	A2	20040128	EP 2002-723359	20020306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005504721	T	20050217	JP 2002-569084	20020306
MX 2003007960	A	20031204	MX 2003-7960	20030904
US 20060030622	A1	20060209	US 2005-236096	20050926
AU 2007231619	A1	20071115	AU 2007-231619	20071023

PRIORITY APPLN. INFO.:	US 2001-273901P	P	20010306
	US 2001-334903P	P	20011024
	AU 2002-254142	A3	20020306
	US 2002-94409	A1	20020306
	WO 2002-US7026	W	20020306

AB The present invention provides methods for treating a variety of urogenital disorders, such as, for example, vaginismus, dyspareunia, vulvodynia (including vulvar vestibulitis), interstitial cystitis, nonspecific urethritis (i.e., nonspecific pain and/or burning of the urinary tract) and sexual dysfunctions, such as, for example, female sexual arousal disorders and female sexual orgasmic disorders, using a variety of compds., including, but not limited to, NO donors, calcium channel blockers, cholinergic modulators, α-adrenergic receptor antagonists, β-adrenergic receptor agonists, phosphodiesterase inhibitors, cAMP-dependent protein kinase activators (e.g., cAMP mimetics), superoxide scavengers, potassium channel activators, estrogen-like compds., testosterone-like compds., benzodiazepines, adrenergic nerve inhibitors, antidiarrheal agents, HMG-CoA reductase inhibitors, smooth muscle relaxants, adenosine receptor modulators, adenylyl cyclase activators, endothelin receptor antagonists, bisphosphonates and cGMP-dependent protein kinase activators (e.g., cGMP mimetics).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:386555 CAPLUS

DOCUMENT NUMBER: 135:356707

TITLE: Effects of antibacterial peptides on mast cell functions

AUTHOR(S): Niyonsaba, Francois; Hirata, Michimasa; Nagaoka, Isao

CORPORATE SOURCE: Department of Biochemistry, School of Medicine, Juntendo University, Japan

SOURCE: Ensho, Saisei (2001), 21(2), 109-115
CODEN: ENSHCC

PUBLISHER: Nippon Ensho-Saisei Igakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Antimicrobial peptides, defensins(human β-defensins, hBDs-1/-2)and LL-37(a peptide of human cathelicidin CAP 18) are expressed at epithelial tissues, where they participate in the innate host defense by killing invaded microorganisms. We have evaluated the effects of hBD-1/-2 and LL-37 on mast cell functions (histamine release and PGD2 production) using rat peritoneal mast cells. The results revealed that hBD-2 and LL-37 but not hBD-1 induced histamine release and intracellular Ca2+ mobilization, and that hBD-2 was more potent than LL-37. Interestingly, histamine release and intracellular Ca2+ mobilization elicited by hBD-2 and LL-37 were markedly suppressed by both pertussis toxin (PTx) and U-73122, a phospholipase C (PLC)inhibitor. In addition, among the peptides examined, only hBD-2 induced PGD2 production that was completely abolished by indomethacin (COX-1/-2 inhibitor)but not NS-398 (COX-2 inhibitor), suggesting that hBD-2-induced PGD2 production is mediated by COX-1 but not COX-2. Likewise, the PGD2 production was completely suppressed by PTx and U-73122. We suggest that hBD-2 and LL-37 activate mast cells to mobilize intracellular Ca2+ and release histamine or generate PGD2 in a G protein-PLC-dependent manner. Thus, hBD-2 and LL-37 may have modulatory effects on inflammatory and allergic reactions by releasing histamine and/or prostanoids from mast cells.

L4 ANSWER 27 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2000:824291 CAPLUS

DOCUMENT NUMBER: 134:21425

TITLE: Protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components

INVENTOR(S): Bridon, Dominique P.; Ezrin, Alan M.; Milner, Peter G.; Holmes, Darren L.; Thibaudeau, Karen

PATENT ASSIGNEE(S): Conjuchem, Inc., Can.

SOURCE: PCT Int. Appl., 733 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069900	A2	20001123	WO 2000-US13576	20000517
WO 2000069900	A3	20010215		
WO 2000069900	A9	20020704		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
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CA 2373252	A1	20001123	CA 2000-2373252	20000517
CA 2373252	C	20070807		
CA 2373680	A1	20001123	CA 2000-2373680	20000517
CA 2373680	C	20080729		
CA 2499211	A1	20001123	CA 2000-2499211	20000517
CA 2501421	A1	20001123	CA 2000-2501421	20000517
CA 2505617	A1	20001123	CA 2000-2505617	20000517
CA 2623458	A1	20001123	CA 2000-2623458	20000517
WO 2000070665	A2	20001123	WO 2000-IB763	20000517
WO 2000070665	A3	20010419		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,				

CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP	1105409	A2	20010613	EP 2000-936023	20000517
EP	1105409	B1	20060301		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
EP	1171582	A2	20020116	EP 2000-929748	20000517
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP	1264840	A1	20021211	EP 2002-14617	20000517
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP	2003500341	T	20030107	JP 2000-619018	20000517
JP	4209086	B2	20090114		
JP	2003508350	T	20030304	JP 2000-618316	20000517
JP	4217004	B2	20090128		
AU	765753	B2	20030925	AU 2000-51393	20000517
EP	1591453	A1	20051102	EP 2005-105384	20000517
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
CN	1698881	A	20051123	CN 2005-10005990	20000517
EP	1598365	A1	20051123	EP 2005-105387	20000517
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
EP	1623994	A2	20060208	EP 2005-108328	20000517
EP	1623994	A3	20080716		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
AT	318835	T	20060315	AT 2000-936023	20000517
PT	1105409	T	20060731	PT 2000-936023	20000517
ES	2257298	T3	20060801	ES 2000-936023	20000517
CN	101289500	A	20081022	CN 2008-10091504	20000517
US	6849714	B1	20050201	US 2000-623548	20000905
US	6514500	B1	20030204	US 2000-657332	20000907
US	7090851	B1	20060815	US 2000-657336	20000907
US	7144854	B1	20061205	US 2000-657431	20000907
ZA	2001006676	A	20020719	ZA 2001-6676	20010814
ZA	2001009110	A	20020613	ZA 2001-9110	20011105
US	20030108567	A1	20030612	US 2002-287892	20021104
US	6821949	B2	20041123		
US	20030108568	A1	20030612	US 2002-288340	20021104
US	6887849	B2	20050503		
US	20040127398	A1	20040701	US 2003-722733	20031125
US	20040138100	A1	20040715	US 2003-723099	20031125
US	20050176641	A1	20050811	US 2005-40810	20050121
US	20050176643	A1	20050811	US 2005-67556	20050225
JP	2005263807	A	20050929	JP 2005-115175	20050412
JP	4219339	B2	20090204		
JP	2005239736	A	20050908	JP 2005-140407	20050512
JP	4221392	B2	20090212		
JP	2005255689	A	20050922	JP 2005-151458	20050524
JP	4116016	B2	20080709		
US	20060009377	A1	20060112	US 2005-170967	20050629
US	20060058235	A1	20060316	US 2005-215967	20050830
JP	2006151986	A	20060615	JP 2005-361126	20051214
US	20060135426	A1	20060622	US 2005-304446	20051214

US 20060135428	A1	20060622	US 2006-350703		20060208
US 20080194486	A1	20080814	US 2007-923222		20071024
US 20080199532	A1	20080821	US 2007-926843		20071029
JP 2008101021	A	20080501	JP 2007-325307		20071217
JP 2008110986	A	20080515	JP 2008-8554		20080117
JP 2008150384	A	20080703	JP 2008-8555		20080117
JP 2009001583	A	20090108	JP 2008-187967		20080718
JP 2009007371	A	20090115	JP 2008-187966		20080718
PRIORITY APPLN. INFO.:			US 1999-134406P	P	19990517
			US 1999-153406P	P	19990910
			US 1999-159783P	P	19991015
			US 1999-134406	A	19990517
			US 1999-153406	A	19990910
			US 1999-159783	A	19991015
			CA 2000-2363712	A3	20000517
			CA 2000-2373680	A3	20000517
			CN 2000-807671	A3	20000517
			EP 2000-932570	A3	20000517
			EP 2000-936023	A3	20000517
			JP 2000-618316	A3	20000517
			JP 2000-618318	A3	20000517
			JP 2000-618327	A3	20000517
			JP 2000-619018	A3	20000517
			WO 2000-IB763	W	20000517
			WO 2000-US13576	W	20000517
			US 2000-623543	A1	20000905
			US 2000-623548	A1	20000905
			US 2000-657276	A2	20000907
			US 2000-657332	A3	20000907
			US 2000-657431	A1	20000907
			US 2002-400199P	P	20020731
			US 2002-400413P	P	20020731
			US 2002-288340	A1	20021104
			WO 2003-CA1097	W	20030729
			US 2003-471348	A1	20030908
			US 2003-722733	A1	20031125
			US 2005-40810	A2	20050121
			US 2005-67556	A1	20050225
			US 2005-170967	A1	20050629
			US 2005-215967	A1	20050830
			JP 2005-361126	A3	20051214

AB A method for protecting a peptide from peptidase activity in vivo, the peptide being composed of between 2 and 50 amino acids and having a C-terminus and an N-terminus and a C-terminus amino acid and an N-terminus amino acid is described. In the first step of the method, the peptide is modified by attaching a reactive group to the C-terminus amino acid, to the N-terminus amino acid, or to an amino acid located between the N-terminus and the C-terminus, such that the modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component. The solid phase peptide synthesis of a number of derivs. with 3-maleimidopropionic acid (3-MPA) is described. In the next step, a covalent bond is formed between the reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity. The final step of the method involves the analyzing of the stability of the peptide-blood component conjugate to assess the protection of the peptide from peptidase activity. Thus, the percentage of a K5 kringle peptide (Pro-Arg-Lys-Leu-Tyr-Asp-Lys-NH2) conjugated to human serum albumin via MPA remained relatively constant through a 24-h plasma assay in contrast to unmodified K5 which decreased to 9% of the original amount of K5 in only 4 h in plasma.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:488366 CAPLUS
DOCUMENT NUMBER: 133:188182
TITLE: Antimicrobial effects of α-MSH peptides
AUTHOR(S): Cutuli, Mariagrazia; Cristiani, Silvia; Lipton, James M.; Catania, Anna
CORPORATE SOURCE: 3rd Division of Internal Medicine, Milan, 20122, Italy
SOURCE: Journal of Leukocyte Biology (2000), 67(2), 233-239
CODEN: JLBIE7; ISSN: 0741-5400
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The presence of the ancient anti-inflammatory peptide α-MSH [α-MSH (1-13), SYSMEHFRWGKPV] in barrier organs such as gut and skin suggests a role in the nonspecific (innate) host defense. α-MSH and its C-terminal tripeptide (11-13, KPV) were determined to have antimicrobial influences against two major and representative pathogens: Staphylococcus aureus and Candida albicans. α-MSH peptides significantly inhibited S. aureus colony formation and reversed the enhancing effect of urokinase on colony formation. Antimicrobial effects occurred over a broad range of concns. including the physiol. (picomolar) range. Small concns. of α-MSH peptides likewise reduced viability and germ tube formation of the yeast C. albicans. Antimicrobial influences of α-MSH peptides could be mediated by their capacity to increase cellular cAMP. Indeed, this messenger was significantly augmented in peptide-treated yeast and the potent adenylyl cyclase inhibitor dideoxyadenosine (ddAdo) partly reversed the killing activity of α-MSH peptides. Reduced killing of pathogens is a detrimental consequence of therapy with anti-inflammatory drugs. Because α-MSH has potent anti-inflammatory effects the authors determined influences of α-MSH on C. albicans and S. aureus killing by human neutrophils. α-MSH peptides did not reduce killing but rather enhanced it, likely as a consequence of the direct antimicrobial activity. α-MSH peptides that combine antipyretic, anti-inflammatory, and antimicrobial effects could be useful in treatment of disorders in which infection and inflammation coexist.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:819393 CAPLUS
DOCUMENT NUMBER: 132:45805
TITLE: Monitoring gene expression or protein levels in evaluating an organism's response to drugs of abuse
INVENTOR(S): Miles, Michael F.; Lai, Chao-qiang; Lockhart, David J.
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967267	A1	19991229	WO 1999-US13839	19990622

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9946963	A	20000110	AU 1999-46963	19990622
US 20060024658	A1	20060202	US 2003-746794	20031223
PRIORITY APPLN. INFO.:			US 1998-90268P	P 19980622
			US 1999-337022	A 19990621
			WO 1999-US13839	W 19990622

AB This invention pertains to the identification of genes whose expression levels are altered by chronic exposure of a cell, tissue, or organism to one or more drugs of abuse (e.g. alc., stimulants, opiates, etc.). In one embodiment, this invention provides a method of monitoring the response of a cell to a drug of abuse. The method involves contacting the cell with the drug of abuse; providing a biol. sample comprising the cell; and detecting, in the sample, the expression of one or more genes or ESTs identified herein, where a difference between the expression of one or more of said genes of ESTs in said sample and one or more of said genes or ESTs in a biol. sample not contacted with said drug of abuse indicates a response of the cell to the drug of abuse. Genes and ESTs whose expression was altered by contact of a cell with EtOH were identified by exposing human neuroblastoma cell line SH-SY5Y-AH1861. Four genes showed a dose-dependent response to EtOH and are therefore believed to represent important targets of EtOH: dopamine β hydroxylase, sodium-dependent norepinephrine transporter, delta-like protein, and monocyte chemoattractant peptide 1. Similar studies were conducted by exposing mice to cocaine. Altered gene expression in the hippocampus, ventral tegmental area, prefrontal cortex, and nucleus accumbens were observed
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 30 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:796403 CAPLUS
DOCUMENT NUMBER: 132:63078
TITLE: β2-Adrenergic receptor stimulation inhibits nitric oxide generation by Mycobacterium avium infected macrophages
AUTHOR(S): Boomershine, Chad S.; Lafuse, William P.; Zwilling, Bruce S.
CORPORATE SOURCE: College of Medicine, The Ohio State University, Columbus, OH, 43210, USA
SOURCE: Journal of Neuroimmunology (1999), 101(1), 68-75
CODEN: JNRIDW; ISSN: 0165-5728
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Catecholamine regulation of nitric oxide (NO) production by IFNγ-primed macrophages infected with M. avium was investigated. Epinephrine treatment of IFNγ-primed, macrophages at the time of M. avium infection inhibited the anti-mycobacterial activity of the cells. The anti-mycobacterial activity of macrophages correlated with NO production Using specific adrenergic receptor agonists, the abrogation of mycobacterial killing and decreased NO production by catecholamines were shown to be mediated via the β2-adrenergic receptor. Elevation of intracellular cAMP levels mimicked the catecholamine-mediated inhibition of NO in both M. avium infected and LPS stimulated macrophages. Specific inhibitors of both adenylate cyclase and protein kinase A prevented the β2-adrenoceptor-mediated inhibition of nitric oxide production

β2-Adrenoreceptor stimulation at the time of M. avium infection of IFNγ-primed macrophages also inhibited expression of iNOS mRNA. Thus, catecholamine hormones can affect the outcome of macrophage-pathogen interactions and one result of sympathetic nervous system activation is the suppression of the capacity of macrophages to produce anti-microbial effector mols.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:677553 CAPLUS
DOCUMENT NUMBER: 127:343737
ORIGINAL REFERENCE NO.: 127:67395a,67398a
TITLE: Rapamycin specifically interferes with the developmental response of fission yeast to starvation
AUTHOR(S): Weisman, R.; Choder, M.; Koltin, Y.
CORPORATE SOURCE: Department of Molecular Microbiology and Biotechnology, Faculty of Life Sciences, Tel Aviv University, Tel Aviv-Jaffa, 69978, Israel
SOURCE: Journal of Bacteriology (1997), 179(20), 6325-6334
CODEN: JOBAAY; ISSN: 0021-9193
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rapamycin is a microbial macrolide which belongs to a family of immunosuppressive drugs that suppress the immune system by blocking stages of signal transduction in T lymphocytes. In Saccharomyces cerevisiae cells, as in T lymphocytes, rapamycin inhibits growth and cells become arrested at the G1 stage of the cell cycle. Rapamycin is also an effective antifungal agent, affecting the growth of yeast and filamentous fungi. Unexpectedly, it was observed that rapamycin has no apparent effect on the vegetative growth of Schizosaccharomyces pombe. Instead, the drug becomes effective only when cells experience starvation. Under such conditions, homothallic wild-type cells will normally mate and undergo sporulation. In the presence of rapamycin, this sexual development process is strongly inhibited and cells adopt an alternative physiol. option and enter stationary phase. Rapamycin strongly inhibits sexual development of haploid cells prior to the stage of sexual conjugation. In contrast, the drug has only a slight inhibitory effect on the sporulation of diploid cells. A genetic approach was applied to identify the signal transduction pathway that is inhibited by rapamycin. The results indicate that either rapamycin did not suppress the derepression of sexual development of strains in which adenylate cyclase was deleted or the cAMP-dependent protein kinase encoded by pka1 was mutated. Nor did rapamycin inhibit the unscheduled meiosis observed in pat1-114 mutants. Overexpression of ras1+, an essential gene for sexual development, did not rescue the sterility of rapamycin-treated cells. However, expression of the activated allele, ras1Val17, antagonized the effect of rapamycin and restored the ability of the cells to respond to mating signals in the presence of the drug. The authors discuss possible mechanisms for the inhibitory effect of rapamycin on sexual development in S. pombe.

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:628435 CAPLUS
DOCUMENT NUMBER: 121:228435
ORIGINAL REFERENCE NO.: 121:41637a,41640a
TITLE: Anthrax edema toxin differentially regulates lipopolysaccharide-induced monocyte production of

tumor necrosis factor alpha and interleukin-6 by increasing intracellular cyclic AMP

AUTHOR(S): Hoover, D. L.; Friedlander, A. M.; Rogers, L. C.; Yoon, I. K.; Warren, R. L.; Cross, A. S.

CORPORATE SOURCE: Dep. Bacterial Diseases, Walter Reed Army Inst. Res., Washington, DC, 20307, USA

SOURCE: Infection and Immunity (1994), 62(10), 4432-9
CODEN: INFIBR; ISSN: 0019-9567

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Bacillus anthracis exotoxins mediate most of the symptomatol. of severe anthrax. In addition to a clin. syndrome reminiscent of septic shock, which may be mediated by cytokines produced by macrophages stimulated with lethal toxin, infected patients show profound edema at sites of infection. Edema is mediated by edema toxin (ET), which comprises of a binding mol., protective antigen, and an active moiety, edema factor, which possesses intrinsic adenylyl cyclase activity. Intracellular cAMP regulates the production of several cytokines that modulate edema formation and play important roles in host defense against invading bacteria. To determine whether ET enhanced the accumulation of cAMP in monocytes and thereby influenced cytokine production, the authors cultured human monocytes with endotoxin [lipopolysaccharide (LPS)] and dilns. of ET and determined the levels of interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) in culture supernatant fluids. The authors further estimated cytokine-specific mRNA accumulation in monocytes by reverse transcription PCR and examined intracellular cAMP concns. following treatment with ET. ET and LPS each induced monocytes to secrete comparable amts. of IL-6. ET did not inhibit and in most expts. modestly enhanced LPS-induced IL-6 production In contrast to this stimulatory effect on IL-6 production, ET induced little or no TNF-α production Moreover, ET profoundly inhibited LPS-induced TNF-α synthesis. These regulatory phenomena were also observed at the mRNA level in association with dose-related enhancement of intracellular cAMP in ET-treated monocytes. Monocytes treated with dibutyryl cAMP, an active analog of cAMP, produced cytokines in a pattern identical to that of cells treated with ET. The disruption of cytokine networks as a consequence of unregulated, ET-induced cAMP accumulation in human monocytes may impair cellular antimicrobial responses and contribute to clin. signs and symptoms.

L4 ANSWER 33 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1993:405014 CAPLUS

DOCUMENT NUMBER: 119:5014

ORIGINAL REFERENCE NO.: 119:1047a,1050a

TITLE: Stimulation of calcium influx and calcium cascade by cyclic AMP in cultured carrot cells

AUTHOR(S): Kurosaki, Fumiya; Nishi, Arasuke

CORPORATE SOURCE: Fac. Pharm. Sci., Toyama Med. Pharm. Univ., Toyama, 930-01, Japan

SOURCE: Archives of Biochemistry and Biophysics (1993), 302(1), 144-51
CODEN: ABBIA4; ISSN: 0003-9861

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Treatment of cultured carrot (Daucus carota) cells with activators of adenylate cyclase, forskolin, and cholera toxin induced the biosynthesis of an antifungal isocoumarin, 6-methoxymellein, in the cells. Addition of dibutyryl cAMP to carrot cell culture also stimulated the accumulation of the compound The cAMP-evoked 6-methoxymellein production was significantly depressed in the presence of certain inhibitors of calcium cascade such as Ca2+ channel blockers and inhibitors of calmodulin-dependent processes. In

dibutyryl cAMP- and forskolin-treated carrot cells, increase in cytosolic Ca2+ concentration was observed as monitored by the fluorescent calcium indicator fluo-3. CAMP-dependent Ca2+ influx into carrot cells was also confirmed with Ca2+-loaded vesicles prepared from the plasma membrane-rich fraction of the cells. Transient increase in Ca2+- and Ca2+/calmodulin-dependent protein kinase activity but not cAMP-dependent protein phosphorylation was detected in the cells of high cAMP concentration Thus, the increase in cAMP content in carrot cells induces Ca2+ influx across plasma membrane without activating cAMP-dependent protein kinase which, then, stimulates calcium cascade in the cells.

L4 ANSWER 34 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1988:146995 CAPLUS
DOCUMENT NUMBER: 108:146995
ORIGINAL REFERENCE NO.: 108:24063a,24066a
TITLE: The effect of azole and polyene antifungals on the plasma membrane enzymes of Candida albicans
AUTHOR(S): Surarit, Rudee; Shepherd, Maxwell G.
CORPORATE SOURCE: Sch. Dent., Univ. Otago, Dunedin, N. Z.
SOURCE: Journal of Medical and Veterinary Mycology (1987), 25(6), 403-13
CODEN: JMVMEO; ISSN: 0268-1218
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The two clin. important classes of antimycotic drugs, the polyenes and azoles, act on the plasma membrane of the cell. The primary modes of action are believed to be through interaction with sterols (polyenes) and alteration in sterol composition of the membrane (azoles). This report shows that, at growth inhibitory concns., the polyenes (nystatin and amphotericin) and azoles (miconazole and ketoconazole) also inhibit plasma membrane enzymes. There was extensive (>75%) inhibition of the Candida albicans plasma membrane enzymes ATPase, glucan synthase, adenyl cyclase, and 5'-nucleotidase, when assayed in situ. The antifungals papulacandin and echinocandin, which inhibit glucan synthesis, also inhibited plasma membrane enzymes in situ; glucan synthase (>90%), 5'-nucleotidase (>80%), and ATPase (70-80%). Purified plasma membrane was prepared from yeast cells of C. albicans by 2 different techniques: concanavalin A stabilization and coating of spheroplasts with silica microbeads. In the purified plasma membrane vesicles prepared from concanavalin A the adenyl cyclase and phosphodiesterase were extensively (>90%) inhibited by the 3 different classes of antifungal drugs; variable inhibition was observed with ATPase (70-100%). The 3',5'-cyclic phosphodiesterase of the plasma membrane purified by the microbead method was almost completely inhibited by all of the antifungals tested and there was partial inhibition of ATPase (20-85%) and adenyl cyclase (30-90%).

L4 ANSWER 35 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1981:459382 CAPLUS
DOCUMENT NUMBER: 95:59382
ORIGINAL REFERENCE NO.: 95:10025a,10028a
TITLE: Purified Clostridium difficile cytotoxin stimulates guanylate cyclase activity and inhibits adenylate cyclase activity
AUTHOR(S): Vesely, David L.; Straub, K. David; Nolan, Charles M.; Rolfe, Rial D.; Finegold, Sydney M.; Monson, Thomas P.
CORPORATE SOURCE: Dep. Med., Univ. Arkansas Med. Sci., Little Rock, AR, 72205, USA
SOURCE: Infection and Immunity (1981), 33(1), 285-91

CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of toxins from 4 strains of C. difficile isolated from patients with pseudomembranous colitis were examined on colonic adenylate (EC 4.6.1.1) and guanylate cyclase (EC 4.6.1.2) activities. Partially purified toxins had a cytotoxic effect on hamster fibroblasts in culture at a concentration of 10 ng/mL. Likewise, these toxins enhanced colonic guanylate cyclase activity 2-3-fold, with the maximal stimulation being at 10 ng/mL. These toxins also enhanced guanylate cyclase activity in ileum, cecum, and duodenum. Both the cytotoxic activity on hamster fibroblasts and the enhancement of hamster guanylate cyclase activity were inhibited by antiserum to C. difficile toxin. These same toxins inhibited adenylate cyclase activity at a 100-ng/mL concentration, but had no effect at 10 ng/mL. They also had no effect at any concentration on colonic Na+-K+ ATPase. To be sure that the finding were not due to acontaminant, a purified C. difficile cytotoxin was used, and the same findings were found with the pure cytotoxin (at a 100-fold-lower concentration). The data suggest that activation of guanylate cyclase may be a factor in the pathogenesis of antimicrobial-associated pseudomembranous colitis.

L4 ANSWER 36 OF 61 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1973:52556 CAPLUS
DOCUMENT NUMBER: 78:52556
ORIGINAL REFERENCE NO.: 78:8257a,8260a
TITLE: Effects of therapeutic agents on cyclic AMP metabolism in vitro
AUTHOR(S): Weinryb, I.; Chasin, M.; Free, C. A.; Harris, D. N.; Goldenberg, H.; Michel, I. M.; Paik, V. S.; Phillips, M.; Samaniego, S.; Hess, S. M.
CORPORATE SOURCE: Dep. Biochem. Pharmacol., Squibb Inst. Med. Res., New Brunswick, NJ, USA
SOURCE: Journal of Pharmaceutical Sciences (1972), 61(10), 1556-67
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One hundred and fifty eight compds. representing 49 classes of therapeutic agents were examined for their effects on steroidogenesis in isolated rat adrenal cells, on lipolysis in isolated rat lipocytes, on the activity of guinea pig lung adenylate cyclase, and on the activity of rat brain and cat heart cyclic nucleotide phosphodiesterase prepns. Classes of drugs active in the central nervous system appeared particularly active in the in vitro systems investigated, as did antiparasitic agents. Experience with general screening of compds. for effects on phosphodiesterase activity, along with data reported here, indicated a correlation between compds. with pharmacol. activity in vivo and inhibition of phosphodiesterase activity in vitro. The data, however, did not provide adequate evidence to decide whether or not the pharmacol. properties of any particular drug in man or animals can be related to an effect on cyclic AMP [60-92-4] metabolism as evidenced in these in vitro systems.

L4 ANSWER 37 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2009079182 MEDLINE
DOCUMENT NUMBER: PubMed ID: 19071134
TITLE: Structure and inhibition of the CO2-sensing carbonic anhydrase Can2 from the pathogenic fungus Cryptococcus neoformans.

AUTHOR: Schlicker Christine; Hall Rebecca A; Vullo Daniela; Middelhaufe Sabine; Gertz Melanie; Supuran Claudiu T; Muhlschlegel Fritz A; Steegborn Clemens
CORPORATE SOURCE: Department of Physiological Chemistry, Ruhr-University Bochum, Universitatsstrasse 150, 44801 Bochum, Germany.
SOURCE: Journal of molecular biology, (2009 Jan 30) Vol. 385, No. 4, pp. 1207-20. Electronic Publication: 2008-11-27. Journal code: 2985088R. E-ISSN: 1089-8638.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-2W3N; PDB-2W3Q
ENTRY MONTH: 200902
ENTRY DATE: Entered STN: 22 Jan 2009
Last Updated on STN: 5 Feb 2009
Entered Medline: 4 Feb 2009

AB In the pathogenic fungus Cryptococcus neoformans, a CO(2)-sensing system is essential for survival in the natural environment (approximately 0.03% CO(2)) and mediates the switch to virulent growth in the human host (approximately 5% CO(2)). This system is composed of the carbonic anhydrase (CA) Can2, which catalyzes formation of bicarbonate, and the fungal, bicarbonate-stimulated adenylyl cyclase Cac1. The critical role of these enzymes for fungal metabolism and pathogenesis identifies them as targets for antifungal drugs. Here, we prove functional similarity of Can2 to the CA Nce103 from Candida albicans and describe its biochemical and structural characterization. The crystal structure of Can2 reveals that the enzyme belongs to the "plant-type" beta-CAs but carries a unique N-terminal extension that can interact with the active-site entrance of the dimer. We further tested a panel of compounds, identifying nanomolar Can2 inhibitors, and present the structure of a Can2 complex with the inhibitor and product analog acetate, revealing insights into interactions with physiological ligands and inhibitors.

L4 ANSWER 38 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2008549708 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18655822
TITLE: Disruption of LH-induced testosterone biosynthesis in testicular Leydig cells by triclosan: probable mechanism of action.
AUTHOR: Kumar Vikas; Balomajumder Chandrajeet; Roy Partha
CORPORATE SOURCE: Molecular Endocrinology Laboratory, Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee 247667, Uttarakhand, India.
SOURCE: Toxicology, (2008 Sep 4) Vol. 250, No. 2-3, pp. 124-31. Electronic Publication: 2008-07-09. Journal code: 0361055. ISSN: 0300-483X.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200811
ENTRY DATE: Entered STN: 30 Aug 2008
Last Updated on STN: 7 Nov 2008
Entered Medline: 6 Nov 2008

AB Triclosan (TCS) is an antimicrobial chemical widely used in different commercial preparations. The present study demonstrated the mechanism of action of TCS-induced anti-androgenicity in rat Leydig cells. Treatment of purified cells with increasing concentrations of TCS (0.001,

0.01, 0.1, 1 and 10 microM) resulted in a significantly decreased activity of adenylyl cyclase enzyme which was followed by a decreased synthesis of cAMP. This decreased cAMP level resulted in the disruption of entire steroidogenic cascade causing a depressed synthesis of testosterone. However, TCS-induced decrease in the production of testosterone returned to normalcy when cells were treated with forskolin (an adenylyl cyclase activator). Transcription followed by translational of four prominent steroidogenic enzyme/proteins, cytochrome P450 side chain cleavage (P450scc), 3beta-hydroxysteroid dehydrogenase (3beta-HSD), 17beta-hydroxysteroid dehydrogenase (17beta-HSD) and steroidogenic acute regulatory (StAR) protein, also decreased in a dose-dependent manner in TCS-treated Leydig cells as determined by RT-PCR, enzyme assay and Western blot. These results suggested that the disruption of the activity of adenylyl cyclase enzyme by TCS in turn leads to the disruption of intermediate steroidogenic cascade causing a depressed testosterone production. The study further confirmed the anti-androgenic activity of TCS in Leydig cells with highest effective concentration at 1 microM.

L4 ANSWER 39 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2008341289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18424546
TITLE: The cyclic AMP-dependent catabolite repression system of Serratia marcescens mediates biofilm formation through regulation of type 1 fimbriae.
AUTHOR: Kalivoda Eric J; Stella Nicholas A; O'Dee Dawn M; Nau Gerard J; Shanks Robert M Q
CORPORATE SOURCE: Charles T. Campbell Laboratory of Ophthalmic Microbiology, Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213, USA.
CONTRACT NUMBER: EY08098 (United States NEI NIH HHS)
SOURCE: Applied and environmental microbiology, (2008 Jun) Vol. 74, No. 11, pp. 3461-70. Electronic Publication: 2008-04-18. Journal code: 7605801. E-ISSN: 1098-5336. Report No.: NLM-PMC2423026.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-EU153350; GENBANK-EU183232
ENTRY MONTH: 200806
ENTRY DATE: Entered STN: 29 May 2008
Last Updated on STN: 27 Jun 2008
Entered Medline: 26 Jun 2008

AB The mechanisms by which environmental carbon sources regulate biofilm formation are poorly understood. This study investigates the roles of glucose and the catabolite repression system in Serratia marcescens biofilm formation. The abilities of this opportunistic pathogen to proliferate in a wide range of environments, to cause disease, and to resist antimicrobials are linked to its ability to form biofilms. We observed that growth of S. marcescens in glucose-rich medium strongly stimulated biofilm formation, which contrasts with previous studies showing that biofilm formation is inhibited by glucose in Escherichia coli and other enteric bacteria. Glucose uptake is known to inversely mediate intracellular cyclic AMP (cAMP) synthesis through regulation of adenylate cyclase (cyaA) activity, which in turn controls fundamental processes such as motility, carbon utilization and storage, pathogenesis, and cell division in many bacteria. Here, we demonstrate that mutation of catabolite repression genes that regulate cAMP levels (crr and cyaA) or the ability to respond to cAMP

(crp) confers a large increase in biofilm formation. Suppressor analysis revealed that phenotypes of a cAMP receptor protein (crp) mutant require the fimABCD operon, which is responsible for type 1 fimbria production. Consistently, fimA transcription and fimbria production were determined to be upregulated in a cyaA mutant background by using quantitative real-time reverse transcription-PCR and transmission electron microscopy analysis. The regulatory pathway by which environmental carbon sources influence cAMP concentrations to alter production of type 1 fimbrial adhesins establishes a novel mechanism by which bacteria control biofilm development.

L4 ANSWER 40 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2008067211 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18221123
TITLE: Diterpenes: a therapeutic promise for cardiovascular diseases.
AUTHOR: Tirapelli Carlos R; Ambrosio Sergio R; da Costa Fernando B; de Oliveira Ana M
CORPORATE SOURCE: Departamento de Enfermagem Psiquiatrica e Ciencias Humanas, Escola de Enfermagem de Ribeirao Preto, USP, Ribeirao Preto, Brazil.
SOURCE: Recent patents on cardiovascular drug discovery, (2008 Jan) Vol. 3, No. 1, pp. 1-8. Ref: 70
Journal code: 101263805. ISSN: 1574-8901.
PUB. COUNTRY: United Arab Emirates
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200803
ENTRY DATE: Entered STN: 29 Jan 2008
Last Updated on STN: 12 Mar 2008
Entered Medline: 11 Mar 2008

AB The research, development and use of natural products as therapeutic agents, especially those derived from plants, have been increasing in recent years. There has been great deal of focus on the naturally occurring antispasmodic phytochemicals as potential therapy for cardiovascular diseases. Naturally occurring diterpenes exert several biological activities such as anti-inflammatory action, antimicrobial and antispasmodic activities. Several diterpenes have been shown to have pronounced cardiovascular effects, for example, grayanotoxin I produces positive inotropic responses, forskolin is a well-known activator of adenylate cyclase, eleganolone and 14-deoxyandrographolide exhibit vasorelaxant properties and marrubenol inhibits smooth muscle contraction by blocking L-type calcium channels. In the last few years, we have investigated the biological activity of kaurane and pimarane-type diterpenes, which are the main secondary metabolites isolated from the roots of Viguiera robusta and V. arenaria, respectively. These diterpenoids exhibit vasorelaxant action and inhibit the vascular contractility mainly by blocking extracellular Ca(2+) influx. Moreover, kaurane and pimarane-type diterpenes decreased mean arterial blood pressure in normotensive rats. Diterpenes likely fulfil the definition of a pharmacological preconditioning class of compounds and give hope for the therapeutic use in cardiovascular diseases. This article will review patents, structure-activity relationship, pharmacology, antihypertensive efficiency, and the vascular mechanisms underlying the effects of diterpenes. Careful examination of the cardiovascular effects exhibited by kaurane and pimarane-type diterpenes will be provided.

L4 ANSWER 41 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2007363158 MEDLINE

DOCUMENT NUMBER: PubMed ID: 17371403
TITLE: Host cell-dependent secretion and translocation of the LepA and LepB effectors of Legionella pneumophila.
AUTHOR: Chen John; Reyes Moraima; Clarke Margaret; Shuman Howard A
CORPORATE SOURCE: Department of Microbiology, Columbia University Medical Center, New York, NY 10032, USA.
CONTRACT NUMBER: AI23549 (United States NIAID NIH HHS)
SOURCE: Cellular microbiology, (2007 Jul) Vol. 9, No. 7, pp. 1660-71. Electronic Publication: 2007-02-16. Journal code: 100883691. ISSN: 1462-5814.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200708
ENTRY DATE: Entered STN: 21 Jun 2007
Last Updated on STN: 22 Aug 2007
Entered Medline: 21 Aug 2007

AB Legionella pneumophila is the Gram-negative bacterial agent of Legionnaires' disease, an acute, often fatal pneumonia. L. pneumophila infects alveolar macrophages, evading the antimicrobial defences of the phagocyte by preventing fusion of the phagosome with lysosomes and avoiding phagosome acidification. The bacteria then modulate the composition of the vacuole so that it takes on the characteristics of the endoplasmic reticulum. Similar events occur when the bacteria infect unicellular protozoa. It is thought that replication in fresh water protozoa provides an environmental reservoir for the organism. Several effector proteins are delivered to the host by the Icm/Dot type IV secretion system (TFSS). Some of these have been shown to participate in the trafficking of the Legionella phagosome. Here we describe the ability of the Icm/Dot TFSS to translocate two effectors, LepA and LepB, that play a role in the non-lytic release of Legionella from protozoa. We report that translocation of the Lep proteins is inhibited by agents that depolymerize actin filaments and that effectors may be secreted into the extracellular medium upon cell contact. Depletion of the Lep proteins by deletion of their genes results in increased ability to lyse red blood cells. In contrast, overexpression of Lep-containing hybrid proteins appears to specifically inhibit the activity of the Icm/Dot TFSS and may prevent the delivery of other effectors that are critical for intracellular multiplication.

L4 ANSWER 42 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2006078724 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16172109
TITLE: Exploiting common targets in human fertilization and HIV infection: development of novel contraceptive microbicides.
AUTHOR: Doncel Gustavo F
CORPORATE SOURCE: CONRAD, Department of Obstetrics and Gynecology, The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, 23507, USA.. doncelgf@evms.edu
SOURCE: Human reproduction update, (2006 Mar-Apr) Vol. 12, No. 2, pp. 103-17. Electronic Publication: 2005-09-19. Ref: 224 Journal code: 9507614. ISSN: 1355-4786.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) General Review; (REVIEW)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 9 Feb 2006
Last Updated on STN: 6 Apr 2006
Entered Medline: 5 Apr 2006

AB The continued high rates of unintended pregnancies and the unrelentless expansion of the acquired immune deficiency syndrome (AIDS) epidemic, especially in less developed countries, warrant the development of novel strategies to help individuals avoid these risks. Dually active compounds displaying contraceptive and microbicidal anti-human immunodeficiency virus (anti-HIV) properties constitute one such strategy. Sharing the same anatomical and functional context, sperm fertilization and genital infection by HIV offer an opportunity for simultaneous intervention. Some of the molecules and mechanisms used by sperm to fertilize the oocyte are similar, if not identical, to those used by HIV while infecting host cells. An example of common structures is the lipid membrane surrounding the spermatozoon and the HIV core. Disruption of its architecture by surface-active compounds exerts both spermicidal and virucidal activity. A more specific alteration of lipid rafts [membrane microdomains enriched in cholesterol and glycosylphosphatidylinositol (GPI)-anchored proteins] by beta-cyclodextrins also results in similar effects. During fertilization and infection, both sperm and HIV interact with their target cell receptors through chemical charges, hydrophobic forces and carbohydrate recognition. Anionic polymers such as cellulose sulphate and polystyrene sulphonate (PSS) inhibit sperm and HIV cell binding. Because some of the molecules involved in this interaction, e.g. heparin sulphate proteoglycan, are also used by other pathogens to infect their target tissues, polyanions exert broad antimicrobial activity as well. During fertilization and infection, sperm and HIV, as well as other microbes, use signal transduction molecules and mechanisms such as adenyl cyclase/cyclic adenosine monophosphate (cAMP)-dependent kinase, calcium and tyrosine phosphorylation, whose inhibition has been shown to impair sperm function and HIV replication. These commonalities at the level of sperm and HIV structure, cell binding and fusion processes, and signalling pathways therefore provide the biological framework to develop bifunctional inhibitors with both antimicrobial and contraceptive properties.

L4 ANSWER 43 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2006031127 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16407097
TITLE: Ras pathway signaling accelerates programmed cell death in the pathogenic fungus Candida albicans.
AUTHOR: Phillips Andrew J; Crowe Jonathan D; Ramsdale Mark
CORPORATE SOURCE: Aberdeen Fungal Group, Institute of Medical Sciences, University of Aberdeen, Foresterhill, AB25 2ZD Aberdeen, Scotland.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2006 Jan 17) Vol. 103, No. 3, pp. 726-31. Electronic Publication: 2006-01-10.
Journal code: 7505876. ISSN: 0027-8424.
Report No.: NLM-PMC1334641.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 19 Jan 2006
Last Updated on STN: 1 Mar 2006
Entered Medline: 28 Feb 2006

AB A better understanding of the molecular basis of programmed cell death (PCD) in fungi could provide information that is useful in the design of antifungal drugs that combat life-threatening fungal infections. Harsh environmental stresses, such as acetic acid or hydrogen peroxide, have been shown to induce PCD in the pathogenic fungus Candida albicans. In this study, we show that dying cells progress from an apoptotic state to a secondary necrotic state and that the rate at which this change occurs is proportional to the intensity of the stimulus. Also, we found that the temporal response is modulated by Ras-cAMP-PKA signals. Mutations that block Ras-cAMP-PKA signaling (ras1Delta, cdc35Delta, tpk1Delta, and tpk2Delta) suppress or delay the apoptotic response, whereas mutations that stimulate signaling (RAS1(val13) and pde2Delta) accelerate the rate of entry of cells into apoptosis. Pharmacological stimulation or inhibition of Ras signaling reinforces these findings. Transient increases in endogenous cAMP occur under conditions that stimulate apoptosis but not growth arrest. Death-specific changes in the abundance of different isoforms of the PKA regulatory subunit, Bcy1p, are also observed. Activation of Ras signals may regulate PCD of C. albicans, either by inhibiting antiapoptotic functions (such as stress responses) or by activating proapoptotic functions.

L4 ANSWER 44 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2005401188 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16043520
TITLE: Calcium-sensing soluble adenylyl cyclase mediates TNF signal transduction in human neutrophils.
AUTHOR: Han Hyunsil; Stessin Alexander; Roberts Julia; Hess Kenneth; Gautam Narinder; Kamenetsky Margarita; Lou Olivia; Hyde Edward; Nathan Noah; Muller William A; Buck Jochen; Levin Lonny R; Nathan Carl
CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021, USA.
CONTRACT NUMBER: AI46382 (United States NIAID NIH HHS)
GM62328 (United States NIGMS NIH HHS)
HD38722 (United States NICHD NIH HHS)
HD42060 (United States NICHD NIH HHS)
HL46849 (United States NHLBI NIH HHS)
HL64774 (United States NHLBI NIH HHS)
SOURCE: The Journal of experimental medicine, (2005 Aug 1) Vol. 202, No. 3, pp. 353-61. Electronic Publication: 2005-07-25.
Journal code: 2985109R. ISSN: 0022-1007.
Report No.: NLM-PMC2213086.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 3 Aug 2005
Last Updated on STN: 30 Sep 2005
Entered Medline: 29 Sep 2005

AB Through chemical screening, we identified a pyrazolone that reversibly blocked the activation of phagocyte oxidase (phox) in human neutrophils in response to tumor necrosis factor (TNF) or formylated peptide. The pyrazolone spared activation of phox by phorbol ester or bacteria, bacterial killing, TNF-induced granule exocytosis and phox assembly, and endothelial transmigration. We traced the pyrazolone's mechanism of action to inhibition of TNF-induced intracellular Ca2+ elevations, and identified a nontransmembrane ("soluble") adenylyl

cyclase (sAC) in neutrophils as a Ca2+-sensing source of cAMP. A sAC inhibitor mimicked the pyrazolone's effect on phox. Both compounds blocked TNF-induced activation of Rap1A, a phox-associated guanosine triphosphatase that is regulated by cAMP. Thus, TNF turns on phox through a Ca2+-triggered, sAC-dependent process that may involve activation of Rap1A. This pathway may offer opportunities to suppress oxidative damage during inflammation without blocking antimicrobial function.

L4 ANSWER 45 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2004381286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15284827
TITLE: Antimycotics suppress interleukin-4 and interleukin-5 production in anti-CD3 plus anti-CD28-stimulated T cells from patients with atopic dermatitis.
AUTHOR: Kanda Naoko
CORPORATE SOURCE: Department of Dermatology, Teikyo University, School of Medicine, 2-11-1 Kaga, Itabashi, Tokyo 173-8605, Japan.
SOURCE: Nihon Ishinkin Gakkai zasshi = Japanese journal of medical mycology, (2004) Vol. 45, No. 3, pp. 137-42. Journal code: 9425640. ISSN: 0916-4804.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (ENGLISH ABSTRACT)
(IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 1 Aug 2004
Last Updated on STN: 29 Sep 2004
Entered Medline: 28 Sep 2004

AB It is reported that antimycotic agents are effective for the treatment of patients with atopic dermatitis (AD). We studied in vitro effects of antimycotics on T helper-1 and T helper-2 cytokine production in anti-CD3 plus anti-CD28-stimulated T cells from AD patients and normal donors. The amounts of interleukin-4 (IL-4) and IL-5 secreted by anti-CD3/CD28-stimulated T cells were higher in AD patients than in normal donors. Azole derivatives, ketoconazole, itraconazole, miconazole and non-azole terbinafine hydrochloride and tolnaftate reduced IL-4 and IL-5 secretion without altering that of IFN-gamma and IL-2 in anti-CD3/CD28-stimulated T cells from both AD patients and normal donors. The azole derivatives were more inhibitory than non-azole antimycotics. These antimycotics reduced the anti-CD3/CD28-induced mRNA expression and promoter activities for IL-4 and IL-5. The cAMP analogue dibutyryl cAMP reversed the inhibitory effects of the antimycotics on IL-4 and IL-5 secretion, mRNA expression, and promoter activities. Anti-CD3/CD28 transiently (< or = 5 min) increased intracellular cAMP in T cells, and the increase was greater in AD patients than in normal donors. The increase of cAMP by anti-CD3/CD28 correlated with IL-4 and IL-5 secretion by anti-CD3/CD28. The transient cAMP increase was suppressed by antimycotics, and azole derivatives were more suppressive than non-azoles. Azole derivatives inhibited the activity of cAMP-synthesizing adenylate cyclase while terbinafine hydrochloride and tolnaftate enhanced the activity of cAMP-hydrolyzing cyclic nucleotide phosphodiesterase in AD and normal T cells. These results suggest that the antimycotics may suppress IL-4 and IL-5 production by reducing cAMP signal, and strengthen the concept of their potential use for the suppression of T helper-2-mediated allergic reactions.

L4 ANSWER 46 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2004309016 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15210817
TITLE: Prostaglandin E2 inhibits alveolar macrophage phagocytosis through an E-prostanoid 2 receptor-mediated increase in intracellular cyclic AMP.
AUTHOR: Aronoff David M; Canetti Claudio; Peters-Golden Marc
CORPORATE SOURCE: Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI 48109-0642, USA.
CONTRACT NUMBER: HL 007749 (United States NHLBI NIH HHS)
HL 058897 (United States NHLBI NIH HHS)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Jul 1) Vol. 173, No. 1, pp. 559-65.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 24 Jun 2004
Last Updated on STN: 18 Aug 2004
Entered Medline: 17 Aug 2004

AB Prostaglandin E(2) is a potent lipid mediator of inflammation that effects changes in cell functions through ligation of four distinct G protein-coupled receptors (E-prostanoid (EP)1, EP2, EP3, and EP4). During pneumonia, PGE(2) production is enhanced. In the present study, we sought to assess the effect of endogenously produced and exogenously added PGE(2) on FcRgamma-mediated phagocytosis of bacterial pathogens by alveolar macrophages (AMs), which are critical participants in lung innate immunity. We also sought to characterize the EP receptor signaling pathways responsible for these effects. PGE(2) (1-1000 nM) dose-dependently suppressed the phagocytosis by rat AMs of IgG-opsonized erythrocytes, immune serum-opsonized Klebsiella pneumoniae, and IgG-opsonized Escherichia coli. Conversely, phagocytosis was stimulated by pretreatment with the cyclooxygenase inhibitor indomethacin. PGE(2) suppression of phagocytosis was associated with enhanced intracellular cAMP production. Experiments using both forskolin (adenylate cyclase activator) and rolipram (phosphodiesterase IV inhibitor) confirmed the inhibitory effect of cAMP stimulation. Immunoblot analysis of rat AMs identified expression of only EP2 and EP3 receptors. The selective EP2 agonist butaprost, but neither the EP1/EP3 agonist sulprostone nor the EP4-selective agonist ONO-AE1-329, mimicked the effects of PGE(2) on phagocytosis and cAMP stimulation. Additionally, the EP2 antagonist AH-6809 abrogated the inhibitory effects of both PGE(2) and butaprost. We confirmed the specificity of our results by showing that AMs from EP2-deficient mice were resistant to the inhibitory effects of PGE(2). Our data support a negative regulatory role for PGE(2) on the antimicrobial activity of AMs, which has important implications for future efforts to prevent and treat bacterial pneumonia.

L4 ANSWER 47 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2003445376 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14506030
TITLE: Cyclic AMP signaling pathway modulates susceptibility of candida species and Saccharomyces cerevisiae to antifungal azoles and other sterol biosynthesis inhibitors.
AUTHOR: Jain Pooja; Akula Indira; Edlind Thomas
CORPORATE SOURCE: Department of Microbiology & Immunology, Drexel University College of Medicine, Philadelphia, Pennsylvania 19129, USA.

CONTRACT NUMBER: AI46768 (United States NIAID NIH HHS)
AI47718 (United States NIAID NIH HHS)
SOURCE: Antimicrobial agents and chemotherapy, (2003 Oct) Vol. 47, No. 10, pp. 3195-201.
Journal code: 0315061. ISSN: 0066-4804.
Report No.: NLM-PMC201163.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 25 Sep 2003
Last Updated on STN: 9 Mar 2004
Entered Medline: 8 Mar 2004

AB Azoles are widely used antifungals; however, their efficacy is compromised by fungistatic activity and selection of resistant strains during treatment. Recent studies demonstrated roles for the protein kinase C and calcium signaling pathways in modulating azole activity. Here we explored a role for the signaling pathway mediated by cyclic AMP (cAMP), which is synthesized by the regulated action of adenylate cyclase (encoded by CDC35 in Candida albicans and CYR1 in Saccharomyces cerevisiae) and cyclase-associated protein (encoded by CAP1 and SRV2, respectively). Relative to wild-type strains, C. albicans and S. cerevisiae strains mutated in these genes were hypersusceptible to fluconazole (>4- to >16-fold-decreased 48-h MIC), itraconazole (>8- to >64-fold), or miconazole (16- to >64-fold). Similarly, they were hypersusceptible to terbinafine and fenpropimorph (2- to >16-fold), which, like azoles, inhibit sterol biosynthesis. Addition of cAMP to the medium at least partially reversed the hypersusceptibility of Ca-cdc35 and Sc-cyr1-2 mutants. An inhibitor of mammalian adenylate cyclase, MDL-12330A, was tested in combination with azoles; a synergistic effect was observed against azole-susceptible and -resistant strains of C. albicans and five of six non-C. albicans Candida species. Analysis of cAMP levels after glucose induction in the presence and absence of MDL-12330A confirmed that it acts by inhibiting cAMP synthesis in yeast. RNA analysis suggested that a defect in azole-dependent upregulation of the multidrug transporter gene CDR1 contributes to the hypersusceptibility of the Ca-cdc35 mutant. Our results implicate cAMP signaling in the yeast azole response; compounds similar to MDL-12330A may be useful adjuvants in azole therapy.

L4 ANSWER 48 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2002471103 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12230500
TITLE: Ketoconazole suppresses interleukin-4 plus anti-CD40-induced IgE class switching in surface IgE negative B cells from patients with atopic dermatitis.
AUTHOR: Kanda Naoko; Watanabe Shinichi
CORPORATE SOURCE: Department of Dermatology, Teikyo University, School of Medicine, Tokyo, Japan.. nmk@med.teikyo-u.ac.jp
SOURCE: The Journal of investigative dermatology, (2002 Sep) Vol. 119, No. 3, pp. 590-9.
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 17 Sep 2002
Last Updated on STN: 11 Oct 2002

Entered Medline: 10 Oct 2002

AB We previously reported that antimycotic agent ketoconazole suppressed interleukin-4 production in T cells from patients with atopic dermatitis. We herein studied if ketoconazole may suppress B cell IgE class switching. Interleukin-4 plus anti-CD40-induced IgE secretion was enhanced in peripheral blood surface IgE- B cells from atopic dermatitis patients compared to those from normal donors, and the secretion was inhibited by ketoconazole. Ketoconazole suppressed interleukin-4 plus anti-CD40-induced germline and mature epsilon transcripts in surface IgE- B cells. Ketoconazole also inhibited interleukin-4 plus anti-CD40-induced activation of germline epsilon promoter in human Burkitt lymphoma Ramos cells. The regions -171/-155 bp containing CCAAT/enhancer-binding protein element and -155/-109 bp containing Stat6 and nuclear factor kappaB elements were required for the ketoconazole-induced inhibition of the germline epsilon promoter activity. Ketoconazole inhibited interleukin-4 plus anti-CD40-induced enhancer activities of CCAAT/enhancer-binding protein and nuclear factor kappaB, and those of composite elements of CCAAT/enhancer-binding protein/Stat6 or of Stat6/nuclear factor kappaB, but did not alter that of Stat6 in Ramos cells. cAMP analog reversed the inhibitory effects of ketoconazole on interleukin-4 plus anti-CD40-induced IgE secretion, germline and mature epsilon transcripts, and epsilon germline promoter activation. Interleukin-4 plus anti-CD40 increased intracellular cAMP by activating cAMP-synthesizing adenylate cyclase in surface IgE- B cells, and the increase was greater in the cells from atopic dermatitis patients than in those from normal donors. Ketoconazole suppressed interleukin-4 plus anti-CD40-induced activation of adenylate cyclase in surface IgE- B cells. These results suggest that ketoconazole may suppress interleukin-4 plus anti-CD40-induced B cell IgE class switching by inhibiting cAMP signal, and stress its prophylactic effects on allergic diseases.

L4 ANSWER 49 OF 61 MEDLINE on STN

ACCESSION NUMBER: 2002411075 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12164941
TITLE: Ketoconazole suppresses prostaglandin E(2)-induced cyclooxygenase-2 expression in human epidermoid carcinoma A-431 cells.
AUTHOR: Kanda Naoko; Watanabe Shinichi
CORPORATE SOURCE: Department of Dermatology, Teikyo University, School of Medicine, 11-1 Kaga-2, Itabashi-Ku, Tokyo 173-8605, Japan.. nmk@med.teikyo-u.ac.jp
SOURCE: The Journal of investigative dermatology, (2002 Jul) Vol. 119, No. 1, pp. 174-81.
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 8 Aug 2002
Last Updated on STN: 18 Sep 2002
Entered Medline: 17 Sep 2002

AB Cyclooxygenase-2 is a key enzyme in the conversion of arachidonic acid to prostaglandins. The overexpression of cyclooxygenase-2 has been reported in skin cancer cells, and may be involved in carcinogenesis. Prostaglandin E2, the end product of cyclooxygenase-2-induced catalysis, autoamplifies the cyclooxygenase-2 expression. It is suggested that an anti-mycotic drug, ketoconazole may inhibit carcinogenesis. We herein investigated if ketoconazole may inhibit prostaglandin

E2-induced cyclooxygenase-2 expression in human epidermoid carcinoma A-431 cells. Ketoconazole suppressed prostaglandin E2-induced cyclooxygenase-2 protein and mRNA expression and promoter activation in A-431; the suppressive effects of ketoconazole were counteracted by cyclic adenosine monophosphate analog. Analyses using deleted or mutated cyclooxygenase-2 promoters revealed that cyclic adenosine monophosphate response element (-59 to - 53 bp) on the promoter was involved in prostaglandin E2-induced stimulation and ketoconazole-induced inhibition of the promoter activity. Electrophoretic mobility shift assays indicated that cyclic adenosine monophosphate response element binding protein and activating transcription factor-1 may constitutively bind to cyclic adenosine monophosphate response element on cyclooxygenase-2 promoter. Prostaglandin E2 increased the proportion of phosphorylated forms among total bound cyclic adenosine monophosphate response element binding protein/activating transcription factor-1, and the effect was suppressed by ketoconazole. Prostaglandin E2 induced the phosphorylation of cyclic adenosine monophosphate response element binding protein and activating transcription factor-1, and the phosphorylation was suppressed by cyclic adenosine monophosphate-dependent protein kinase (protein kinase A) inhibitor, indicating protein kinase A-mediated phosphorylation. Ketoconazole suppressed the prostaglandin E2-induced phosphorylation of cyclic adenosine monophosphate response element binding protein/activating transcription factor-1. Prostaglandin E2 increased intracellular cyclic adenosine monophosphate level by activating adenylate cyclase in A-431, and the increase was suppressed by ketoconazole. These results suggest that ketoconazole may suppress prostaglandin E2-induced cyclooxygenase-2 expression by inhibiting the cyclic adenosine monophosphate signal in A-431, and stress its anti-cancer effect.

L4 ANSWER 50 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2002338978 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12081150
TITLE: Effects of ketoconazole on progesterone and cAMP production in MA-10 mouse Leydig tumor cells.
AUTHOR: Chang Cicero Lee-Tian; Fung Hang-Poung
CORPORATE SOURCE: Department of Veterinary Medicine, College of Veterinary Medicine, National Chang Hsing University, Taichung, Taiwan, ROC.. d8538002@mail.nchu.edu.tw
SOURCE: Biological & pharmaceutical bulletin, (2002 Jun) Vol. 25, No. 6, pp. 794-7.
Journal code: 9311984. ISSN: 0918-6158.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 26 Jun 2002
Last Updated on STN: 2 Jan 2003
Entered Medline: 31 Dec 2002

AB The effects of ketoconazole (KCZ) on secretion of progesterone and cAMP in Leydig cells were investigated in vitro. MA-10 mouse Leydig tumor cells were used to conduct the experiments. KCZ significantly inhibited the progesterone production from MA-10 cells in a dose dependent fashion between 2 and 20 microM among 1, 2 and 3 h of incubation. There was a statistically significant difference in luteinizing hormone (LH) stimulated progesterone production inhibited by 2 and 20 microm KCZ treatment compared to the control. The effect of KCZ on progesterone biosynthesis in MA-10 cells was mediated by cAMP, since KCZ suppressed basal and LH stimulated cAMP production and content within the same dose range. The stimulatory effects of forskolin and sodium fluoride on the adenylate cyclase system were also inhibited

by KCZ. Moreover, dibutyryl cAMP blocked the inhibitory effect on steroidogenesis of KCZ in MA-10 cells. These data indicated that KCZ induced the inhibition of a catalytic component of adenylate cyclase holoenzyme in MA-10 mouse Leydig tumor cells.

L4 ANSWER 51 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2002152872 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11886533
TITLE: Anti-mycotics suppress interleukin-4 and interleukin-5 production in anti-CD3 plus anti-CD28-stimulated T cells from patients with atopic dermatitis.
AUTHOR: Kanda N; Enomoto U; Watanabe S
CORPORATE SOURCE: Department of Dermatology, Teikyo University, School of Medicine, Japan.. nmk@med.teikyo-u.ac.jp
SOURCE: The Journal of investigative dermatology, (2001 Dec) Vol. 117, No. 6, pp. 1635-46.
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 12 Mar 2002
Last Updated on STN: 6 Apr 2002
Entered Medline: 5 Apr 2002

AB It is reported that anti-mycotic agents are effective for the treatment of patients with atopic dermatitis. We studied the in vitro effects of anti-mycotics on T helper-1 and T helper-2 cytokine production in anti-CD3 plus anti-CD28-stimulated T cells from atopic dermatitis patients and normal donors. The amounts of interleukin-4 and interleukin-5 secreted by anti-CD3/CD28-stimulated T cells were higher in atopic dermatitis patients than in normal donors. Azole derivatives, ketoconazole, itraconazole, miconazole, and nonazole terbinafine hydrochloride, and tolnaftate reduced interleukin-4 and interleukin-5 secretion without altering that of interferon-gamma and interleukin-2 in anti-CD3/CD28-stimulated T cells from both atopic dermatitis patients and normal donors. The azole derivatives were more inhibitory than nonazole anti-mycotics. These anti-mycotics reduced the anti-CD3/CD28-induced mRNA expression and promoter activities for interleukin-4 and interleukin-5. The 3',5'-cyclic adenosine monophosphate analog dibutyryl 3',5'-cyclic adenosine monophosphate reversed the inhibitory effects of the anti-mycotics on interleukin-4 and interleukin-5 secretion, mRNA expression, and promoter activities. Anti-CD3/CD28 transiently (< or = 5 min) increased intracellular 3',5'-cyclic adenosine monophosphate in T cells, and the increase was greater in atopic dermatitis patients than in normal donors. The increase of 3',5'-cyclic adenosine monophosphate by anti-CD3/CD28 correlated with interleukin-4 and interleukin-5 secretion by anti-CD3/CD28. The transient 3',5'-cyclic adenosine monophosphate increase was suppressed by anti-mycotics, and azole derivatives were more suppressive than nonazoles. Azole derivatives inhibited the activity of cyclic adenosine monophosphate-synthesizing adenylate cyclase whereas terbinafine hydrochloride and tolnaftate enhanced the activity of 3',5'-cyclic adenosine monophosphate-hydrolyzing cyclic nucleotide phosphodiesterase in atopic dermatitis and normal T cells. These results suggest that the anti-mycotics may suppress interleukin-4 and interleukin-5 production by reducing 3',5'-cyclic adenosine monophosphate signal, and stress their potential use for the suppression of T helper-2-mediated allergic reactions.

L4 ANSWER 52 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2000408910 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10939337
TITLE: Tetanic stimulation recruits vesicles from reserve pool via a cAMP-mediated process in Drosophila synapses.
AUTHOR: Kuromi H; Kidokoro Y
CORPORATE SOURCE: Institute for Behavioral Sciences, Gunma University School of Medicine, Maebashi, Japan.. kuromi@med.gunma-u.ac.jp
SOURCE: Neuron, (2000 Jul) Vol. 27, No. 1, pp. 133-43.
Journal code: 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 7 Sep 2000
Last Updated on STN: 7 Sep 2000
Entered Medline: 28 Aug 2000

AB At Drosophila neuromuscular junctions, there are two synaptic vesicle pools, namely the exo/endo cycling pool (ECP) and the reserve pool (RP). We studied the recruitment process from RP using a fluorescent dye, FMI-43. During high-frequency nerve stimulation, vesicles in RP were recruited for release, and endocytosed vesicles were incorporated into both pools, whereas with low-frequency stimulation, vesicles were incorporated into and released from ECP. Release of vesicles from RP was detected electrophysiologically after emptying vesicles in the ECP of transmitter by a H+ pump inhibitor. Recruitment from RP was depressed by inhibitors of steps in the cAMP/PKA cascade and enhanced by their activators. In rutabaga (rut) with low cAMP levels, mobilization of vesicles from RP during tetanic stimulation was depressed, while it was enhanced in dunce (dnc) with high cAMP levels.

L4 ANSWER 53 OF 61 MEDLINE on STN
ACCESSION NUMBER: 2000134045 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10670585
TITLE: Antimicrobial effects of alpha-MSH peptides.
AUTHOR: Cutuli M; Cristiani S; Lipton J M; Catania A
CORPORATE SOURCE: 3rd Division of Internal Medicine, IRCCS Ospedale Maggiore, Milano, Italy.
CONTRACT NUMBER: NS10046 (United States NINDS NIH HHS)
SOURCE: Journal of leukocyte biology, (2000 Feb) Vol. 67, No. 2, pp. 233-9.
Journal code: 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 9 Mar 2000
Last Updated on STN: 9 Mar 2000
Entered Medline: 24 Feb 2000

AB The presence of the ancient anti-inflammatory peptide alpha-melanocyte-stimulating hormone [alpha-MSH (1-13), SYSMEHFRWGKPV] in barrier organs such as gut and skin suggests a role in the nonspecific (innate) host defense. alpha-MSH and and its carboxy-terminal tripeptide (11-13, KPV) were determined to have antimicrobial influences against two major and representative pathogens: Staphylococcus aureus and Candida albicans. alpha-MSH peptides significantly inhibited S. aureus colony formation and reversed the enhancing effect of urokinase on colony formation. Antimicrobial effects occurred over a broad

range of concentrations including the physiological (picomolar) range. Small concentrations of alpha-MSH peptides likewise reduced viability and germ tube formation of the yeast C. albicans. Antimicrobial influences of alpha-MSH peptides could be mediated by their capacity to increase cellular cAMP. Indeed, this messenger was significantly augmented in peptide-treated yeast and the potent adenylyl cyclase inhibitor dideoxyadenosine (ddAdo) partly reversed the killing activity of alpha-MSH peptides. Reduced killing of pathogens is a detrimental consequence of therapy with anti-inflammatory drugs. Because alpha-MSH has potent anti-inflammatory effects we determined influences of alpha-MSH on C. albicans and S. aureus killing by human neutrophils. alpha-MSH peptides did not reduce killing but rather enhanced it, likely as a consequence of the direct antimicrobial activity. alpha-MSH peptides that combine antipyretic, anti-inflammatory, and antimicrobial effects could be useful in treatment of disorders in which infection and inflammation coexist.

L4 ANSWER 54 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1998022028 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9379122
TITLE: Phosphoserine/threonine phosphatases in the rat adrenal cortex: a role in the control of steroidogenesis?.
AUTHOR: Sayed S B; Whitehouse B J; Jones P M
CORPORATE SOURCE: Cellular and Molecular Endocrinology Group, King's College London, UK.
SOURCE: The Journal of endocrinology, (1997 Sep) Vol. 154, No. 3, pp. 449-58.
Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 24 Dec 1997
Last Updated on STN: 24 Dec 1997
Entered Medline: 10 Nov 1997

AB The involvement of protein kinases in the signal transduction pathways controlling adrenal steroidogenesis is well established, and the phosphorylation of substrates by cAMP-dependent protein kinase is a major mechanism in ACTH action. However, the possibility that protein phosphatases (PPs) might also be involved in this process has not been investigated. The aim of this study was, therefore, to measure the function, expression and enzymic activity of PPs in zona glomerulosa (ZG) and zona fasciculata/reticularis (ZFR) tissue from the rat adrenal cortex. Immunoblot analysis using specific antisera demonstrated the presence in whole adrenals and capsules of PP type 1 (PP1) migrating with an apparent molecular mass of 37 kDa, and PP type 2A (PP2A) migrating with apparent molecular masses of 38 and 31 kDa. The PP inhibitors, okadaic acid (OA), calyculin A (CA), tautomycin and microcystin RR, caused a reduction in PP activity in vitro, at doses between 1 nM and 1 microM. In addition, treatment of ZG cells with the adenylate cyclase stimulator, forskolin (10 microM) resulted in a significant reduction in PP activity. The effects of CA and OA on steroid secretion by ZG and ZFR cells were also investigated. Neither CA nor OA had any effect on basal steroid secretion or on yields of steroid obtained from 22R-hydroxycholesterol at doses between 1 and 100 nM. However, both OA and CA (10 and 100 nM respectively) significantly reduced ACTH-stimulated aldosterone and corticosterone production by ZG and ZFR cells. CA and OA (10 and 100 nM respectively) also reduced steroid secretion by cells stimulated by forskolin (10 microM) or dibutyryl cAMP (200 microM). These results suggest that PPs may be involved in the

intracellular mechanisms through which adrenocortical steroidogenesis is regulated, acting at a point after cAMP generation and action, but proximal to the side-chain cleavage of cholesterol.

L4 ANSWER 55 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1997474255 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9335279
TITLE: Rapamycin specifically interferes with the developmental response of fission yeast to starvation.
AUTHOR: Weisman R; Choder M; Koltin Y
CORPORATE SOURCE: Department of Molecular Microbiology and Biotechnology, Faculty of Life Sciences, Tel Aviv University, Israel.. ronitt@post.tau.ac.il
SOURCE: Journal of bacteriology, (1997 Oct) Vol. 179, No. 20, pp. 6325-34.
Journal code: 2985120R. ISSN: 0021-9193.
Report No.: NLM-PMC179546.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 24 Dec 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 4 Nov 1997

AB Rapamycin is a microbial macrolide which belongs to a family of immunosuppressive drugs that suppress the immune system by blocking stages of signal transduction in T lymphocytes. In Saccharomyces cerevisiae cells, as in T lymphocytes, rapamycin inhibits growth and cells become arrested at the G1 stage of the cell cycle. Rapamycin is also an effective antifungal agent, affecting the growth of yeast and filamentous fungi. Unexpectedly, we observed that rapamycin has no apparent effect on the vegetative growth of Schizosaccharomyces pombe. Instead, the drug becomes effective only when cells experience starvation. Under such conditions, homothallic wild-type cells will normally mate and undergo sporulation. In the presence of rapamycin, this sexual development process is strongly inhibited and cells adopt an alternative physiological option and enter stationary phase. Rapamycin strongly inhibits sexual development of haploid cells prior to the stage of sexual conjugation. In contrast, the drug has only a slight inhibitory effect on the sporulation of diploid cells. A genetic approach was applied to identify the signal transduction pathway that is inhibited by rapamycin. The results indicate that either rapamycin did not suppress the derepression of sexual development of strains in which adenylate cyclase was deleted or the cyclic AMP-dependent protein kinase encoded by pka1 was mutated. Nor did rapamycin inhibit the unscheduled meiosis observed in pat1-114 mutants. Overexpression of ras1+, an essential gene for sexual development, did not rescue the sterility of rapamycin-treated cells. However, expression of the activated allele, ras1Val17, antagonized the effect of rapamycin and restored the ability of the cells to respond to mating signals in the presence of the drug. We discuss possible mechanisms for the inhibitory effect of rapamycin on sexual development in S. pombe.

L4 ANSWER 56 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1995402577 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7545625
TITLE: Inhibition of serine/threonine protein phosphatases enhances agonist-stimulated cAMP accumulation in UMR 106 osteoblast-like cells.

AUTHOR: Kovacs C S; Chik C L; Li B; Karpinski E; Ho A K
CORPORATE SOURCE: Department of Medicine, University of Alberta, Edmonton, Canada.
SOURCE: Molecular and cellular endocrinology, (1995 Apr 28) Vol. 110, No. 1-2, pp. 9-16.
Journal code: 7500844. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 26 Oct 1995
Last Updated on STN: 29 Jan 1996
Entered Medline: 18 Oct 1995

AB Protein phosphatases regulate the activity of signal transduction mechanisms by dephosphorylating activated components. By utilizing selective inhibitors of these phosphatases, we investigated their role in regulating cAMP accumulation in the UMR 106 osteoblast-like tumor cell line. PTHrP, PTH and PGE2 stimulated cAMP accumulation up to 100-fold. Calyculin A, a potent inhibitor of protein phosphatase type 1 (PP1) and type 2A (PP2A), did not affect basal levels of cAMP, but concentrations of 10(-11) M to 10(-8) M increased PTHrP-, PTH-, and PGE2-stimulated cAMP accumulation up to 1.7-fold, and this increase was concentration-dependent. Similar results were obtained with tautomycin, another potent inhibitor of PP1 and PP2A. In contrast, okadaic acid, a potent inhibitor of PP2A which inhibited PP1 less potently, did not enhance PTHrP-, PTH-, or PGE2-stimulated cAMP accumulation. The effect of calyculin A on agonist-stimulated cAMP accumulation persisted in cells treated with isobutyl methylxanthine, a phosphodiesterase inhibitor. When the effect of calyculin A was compared with that of 4 beta-phorbol 12-myristate 13-acetate (PMA), it was found that while PMA enhanced both the receptor and forskolin-stimulated cAMP accumulation, calyculin A had no effect on the forskolin-stimulated cAMP accumulation. The effect of calyculin A on PTHrP- and PTH-stimulated cAMP accumulation persisted in cells treated with PMA. These results suggest that protein phosphatases play an important role in agonist-stimulated cAMP accumulation in osteoblast-like cells, and that PP1 but not PP2A may be the major phosphatase involved. In contrast to activation by protein kinase C, the site of action for the phosphatase appears to be predominantly at a step prior to the activation of adenylyl cyclase in the cAMP signal transduction pathway.

L4 ANSWER 57 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1995012633 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7927706
TITLE: Anthrax edema toxin differentially regulates lipopolysaccharide-induced monocyte production of tumor necrosis factor alpha and interleukin-6 by increasing intracellular cyclic AMP.
AUTHOR: Hoover D L; Friedlander A M; Rogers L C; Yoon I K; Warren R L; Cross A S
CORPORATE SOURCE: Department of Bacterial Diseases, Walter Reed Army Institute of Research, Washington, D.C. 20307.
SOURCE: Infection and immunity, (1994 Oct) Vol. 62, No. 10, pp. 4432-9.
Journal code: 0246127. ISSN: 0019-9567.
Report No.: NLM-PMC303127.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 22 Dec 1994
Last Updated on STN: 22 Dec 1994
Entered Medline: 4 Nov 1994

AB Bacillus anthracis exotoxins mediate most of the symptomatology of severe anthrax. In addition to a clinical syndrome reminiscent of septic shock, which may be mediated by cytokines produced by macrophages stimulated with lethal toxin, infected patients show profound edema at sites of infection. Edema is mediated by edema toxin (ET), which comprises of a binding molecule, protective antigen, and an active moiety, edema factor, which possesses intrinsic adenylyl cyclase activity.
Intracellular cyclic AMP (cAMP) regulates the production of several cytokines that modulate edema formation and play important roles in host defense against invading bacteria. To determine whether ET enhanced the accumulation of cAMP in monocytes and thereby influenced cytokine production, we cultured human monocytes with endotoxin (lipopolysaccharide [LPS]) and dilutions of ET and determined the levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) in culture supernatant fluids. We further estimated cytokine-specific mRNA accumulation in monocytes by reverse transcription PCR and examined intracellular cAMP concentrations following treatment with ET. ET and LPS each induced monocytes to secrete comparable amounts of IL-6. ET did not inhibit and in most experiments modestly enhanced LPS-induced IL-6 production. In contrast to this stimulatory effect on IL-6 production, ET induced little or no TNF-alpha production. Moreover, ET profoundly inhibited LPS-induced TNF-alpha synthesis. These regulatory phenomena were also observed at the mRNA level in association with dose-related enhancement of intracellular cAMP in ET-treated monocytes. Monocytes treated with dibutyryl cAMP, an active analog of cAMP, produced cytokines in a pattern identical to that of cells treated with ET. The disruption of cytokine networks as a consequence of unregulated, ET-induced cAMP accumulation in human monocytes may impair cellular antimicrobial responses and contribute to clinical signs and symptoms.

L4 ANSWER 58 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1993228336 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8385897
TITLE: Stimulation of calcium influx and calcium cascade by cyclic AMP in cultured carrot cells.
AUTHOR: Kurosaki F; Nishi A
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Japan.
SOURCE: Archives of biochemistry and biophysics, (1993 Apr) Vol. 302, No. 1, pp. 144-51.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 21 May 1993
Last Updated on STN: 6 Feb 1998
Entered Medline: 12 May 1993

AB Treatment of cultured carrot (Daucus carota L.) cells with activators of adenylate cyclase, forskolin, and cholera toxin induced the biosynthesis of an antifungal isocoumarin, 6-methoxymellein, in the cells. Addition of dibutyryl cyclic AMP to carrot cell culture also stimulated the accumulation of the compound. The cyclic AMP-evoked 6-methoxymellein production was significantly depressed in the presence of certain inhibitors of calcium cascade such as Ca2+ channel

blockers and inhibitors of calmodulin-dependent processes. In dibutyryl cyclic AMP- and forskolin-treated carrot cells, increase in cytosolic Ca2+ concentration was observed as monitored by the fluorescent calcium indicator fluo-3. Cyclic AMP-dependent Ca2+ influx into carrot cells was also confirmed with Ca(2+)-loaded vesicles prepared from the plasma membrane-rich fraction of the cells. Transient increase in Ca(2+)- and Ca2+/calmodulin-dependent protein kinase activity but not cyclic AMP-dependent protein phosphorylation was detected in the cells of high cyclic AMP concentration. Results obtained in the present work suggest that the increase in cyclic AMP content in carrot cells induces Ca2+ influx across plasma membrane without activating cyclic AMP-dependent protein kinase which, then, stimulates calcium cascade in the cells.

L4 ANSWER 59 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1988141010 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2830394
TITLE: The effects of azole and polyene antifungals on the plasma membrane enzymes of Candida albicans.
AUTHOR: Surarit R; Shepherd M G
CORPORATE SOURCE: Experimental Oral Biology Unit, School of Dentistry, University of Otago, Dunedin, New Zealand.
SOURCE: Journal of medical and veterinary mycology : bi-monthly publication of the International Society for Human and Animal Mycology, (1987 Dec) Vol. 25, No. 6, pp. 403-13. Journal code: 8605493. ISSN: 0268-1218.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 25 Mar 1988

AB The two clinically important classes of antimycotic drugs, the polyenes and azoles, act on the plasma membrane of the cell. The primary modes of action are believed to be through interaction with sterols (polyenes) and alteration in sterol composition of the membrane (azoles). In this report we show that, at growth inhibitory concentrations, the polyenes (nystatin and amphotericin) and azoles (miconazole and ketoconazole) also inhibit plasma membrane enzymes. There was extensive (greater than 75%) inhibition of the Candida albicans plasma membrane enzymes ATPase, glucan synthase, adenyl cyclase and 5'-nucleotidase, when assayed in situ. The antifungals papulacandin and echinocandin, which inhibit glucan synthesis, also inhibited plasma membrane enzymes in situ; glucan synthase (greater than 90%), 5'-nucleotidase (greater than 80%) and ATPase (70-80%). Purified plasma membrane was prepared from yeast cells of C. albicans by two different techniques: concanavalin A stabilization and coating of spheroplasts with silica microbeads. In the purified plasma membrane vesicles prepared from concanavalin A the adenyl cyclase and phosphodiesterase were extensively (greater than 90%) inhibited by the three different classes of antifungal drugs; variable inhibition was observed with ATPase (70-100%). The 3',5'-cyclic phosphodiesterase of the plasma membrane purified by the microbeads method was almost completely inhibited by all of the antifungals tested and there was partial inhibition of ATPase (20-85%) and adenyl cyclase (30-90%).

L4 ANSWER 60 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1981263035 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6114928

TITLE: Purified Clostridium difficile cytotoxin stimulates guanylate cyclase activity and inhibits adenylate cyclase activity.
AUTHOR: Vesely D L; Straub K D; Nolan C M; Rolfe R D; Finegold S M; Monson T P
SOURCE: Infection and immunity, (1981 Jul) Vol. 33, No. 1, pp. 285-91.
Journal code: 0246127. ISSN: 0019-9567.
Report No.: NLM-PMC350687.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198110
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 25 Oct 1981

AB Antibiotic-associated pseudomembranous colitis has been linked with Clostridium difficile toxin. We examined the effect of toxins from four strains of C. difficile isolated from patients with pseudomembranous colitis on colonic adenylate (EC 4.6.1.1) and guanylate cyclase (EC 4.6.1.2) activities. Partially purified toxins had a cytotoxic effect on hamster fibroblasts in culture at a concentration of 10 ng/ml. Likewise, these toxins enhanced colonic guanylate cyclase activity two- to threefold, with the maximal stimulation being at 10 ng/ml. These toxins also enhanced guanylate cyclase activity in ileum, cecum, and duodenum. Both the cytotoxic activity on hamster fibroblasts and the enhancement of hamster guanylate cyclase activity were inhibited by antiserum to C. difficile toxin. These same toxins inhibited adenylate cyclase activity at a 100-ng/ml concentration, but had no effect at 10 ng/ml. They also had no effect at any concentration on colonic Na+-K+ adenosine triphosphatase. To be sure that the findings were not due to a contaminant, a purified C. difficile cytotoxin was used, and the same findings were found with the pure cytotoxin (at a 100-fold-lower concentration). The data suggest that activation of guanylate cyclase may be a factor in the pathogenesis of antimicrobial-associated pseudomembranous colitis.

L4 ANSWER 61 OF 61 MEDLINE on STN
ACCESSION NUMBER: 1974169548 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4830243
TITLE: Uncoupling of catecholamine activation of pigeon erythrocyte membrane adenylate cyclase by filipin.
AUTHOR: Puchwein G; Pfeuffer T; Helmreich E J
SOURCE: The Journal of biological chemistry, (1974 May 25) Vol. 249, No. 10, pp. 3232-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197407
ENTRY DATE: Entered STN: 10 Mar 1990
Last Updated on STN: 10 Mar 1990
Entered Medline: 20 Jul 1974

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NEWS 14	FEB 10	COMPENDEX reloaded and enhanced
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=> e calmidazolium
E1            4     CALMID/BI
E2            4     CALMIDAZOL/BI
E3            4 --> CALMIDAZOLIUM/BI
E4           16     CALMIN/BI
E5            1     CALMINAL/BI
E6            1     CALMIPAN/BI
E7            1     CALMIREN/BI
E8            2     CALMITIN/BI
E9            4     CALMITINE/BI
E10           1     CALMIVET/BI
E11           1     CALMIXEN/BI
E12           2     CALML3/BI

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=> s e3
L1            4 CALMIDAZOLIUM/BI

=> d l1 1-4

L1   ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   188061-61-2  REGISTRY
ED   Entered STN:  09 Apr 1997
CN   1H-Imidazolium, 3-[bis(4-chlorophenyl)methyl]-1-[(2R)-2-(2,4-
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(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Imidazolium, 1-[bis(4-chlorophenyl)methyl]-3-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, chloride, (R)- (9CI)
OTHER NAMES:
CN (-)-(R)-Calmidazolium chloride
FS STEREOSEARCH
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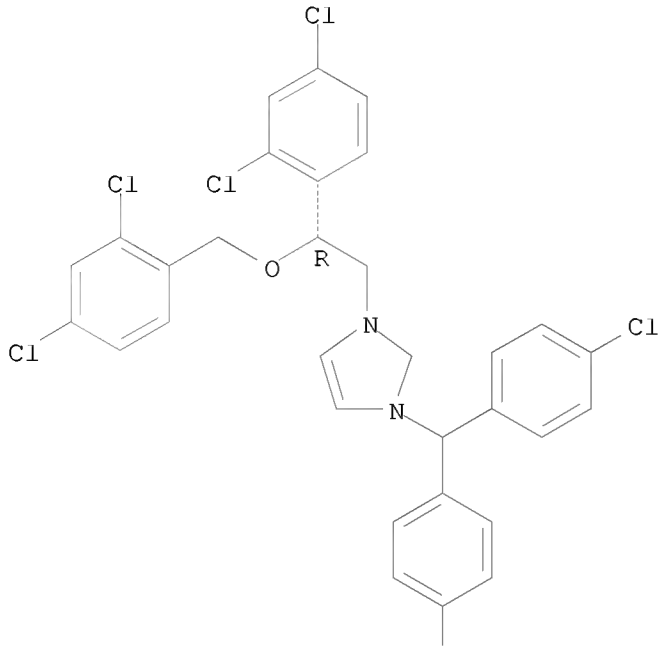
CRN (767267-52-7)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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1 REFERENCES IN FILE CA (1907 TO DATE)
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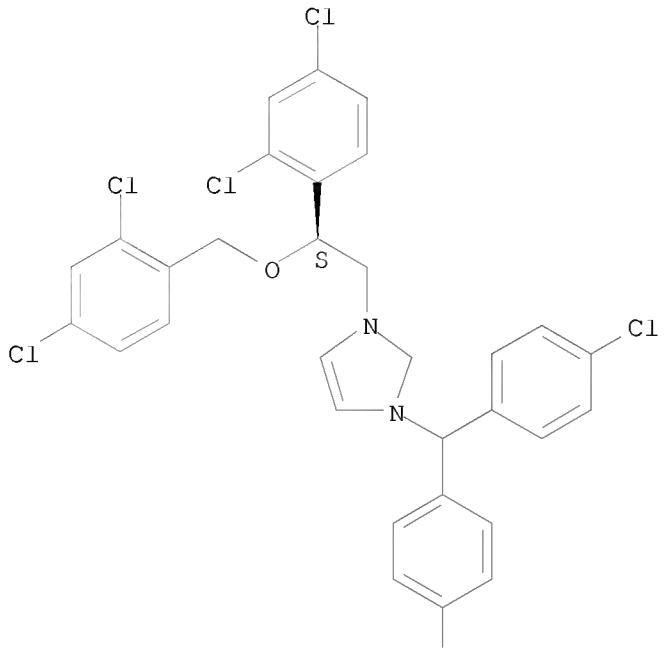
L1 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2009 ACS on STN
RN 188061-60-1 REGISTRY
ED Entered STN: 09 Apr 1997
CN 1H-Imidazolium, 3-[bis(4-chlorophenyl)methyl]-1-[(2S)-2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, chloride (1:1)
(CA INDEX NAME)

OTHER CA INDEX NAMES:
CN 1H-Imidazolium, 1-[bis(4-chlorophenyl)methyl]-3-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, chloride, (S)- (9CI)
OTHER NAMES:
CN (+)-(S)-Calmidazolium chloride
FS STEREOSEARCH
MF C31 H23 Cl6 N2 O . Cl
SR CA
LC STN Files: CA, CAPLUS
CRN (773829-12-2)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



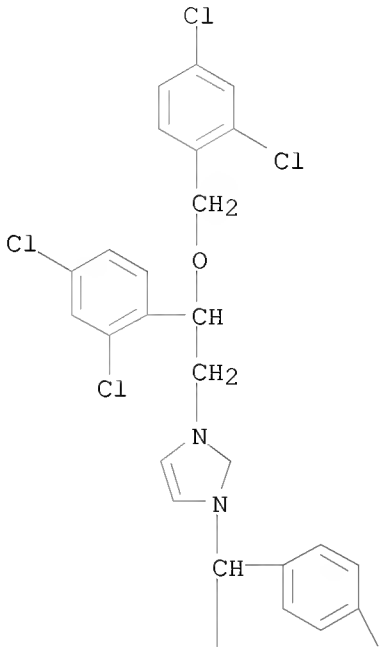
PAGE 2-A

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

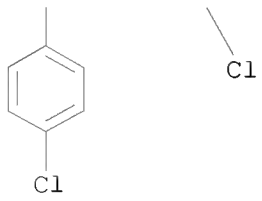
L1 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2009 ACS on STN
RN 95013-41-5 REGISTRY
ED Entered STN: 03 Mar 1985
CN 1H-Imidazolium, 3-[bis(4-chlorophenyl)methyl]-1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Imidazolium, 1-[bis(4-chlorophenyl)methyl]-3-[2-(2,4-dichlorophenyl)-2-

[(2,4-dichlorophenyl)methoxy]ethyl]- (9CI)
OTHER NAMES:
CN Calmidazolium
DR 97992-02-4
MF C31 H23 Cl6 N2 O
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CSCHEM, EMBASE, PHAR, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

PAGE 1-A



PAGE 2-A

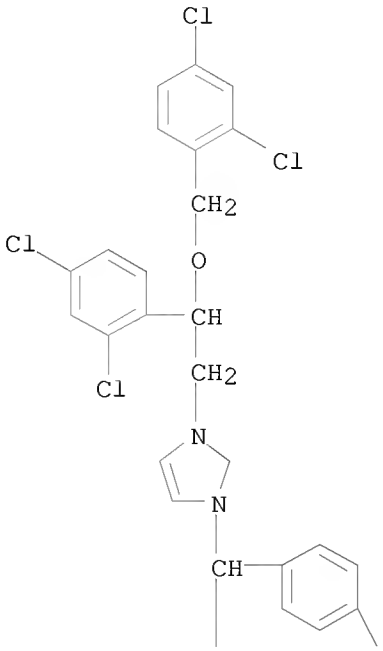


ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE
237 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
238 REFERENCES IN FILE CAPLUS (1907 TO DATE)

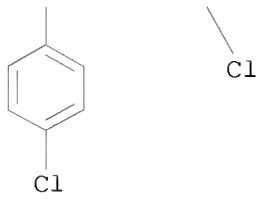
L1 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2009 ACS on STN
RN 57265-65-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1H-Imidazolium, 3-[bis(4-chlorophenyl)methyl]-1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, chloride (1:1) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Imidazolium, 1-[bis(4-chlorophenyl)methyl]-3-[2-(2,4-dichlorophenyl)-2-

[(2,4-dichlorophenyl)methoxy]ethyl]-, chloride (9CI)
OTHER NAMES:
CN Calmidazolium chloride
CN R 24571
MF C31 H23 Cl6 N2 O . Cl
LC STN Files: BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, PHAR, TOXCENTER, USPAT2, USPATFULL
CRN (95013-41-5)

PAGE 1-A



PAGE 2-A



● Cl⁻

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE
116 REFERENCES IN FILE CA (1907 TO DATE)
116 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus medline
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

FULL ESTIMATED COST 14.03 14.25

FILE 'CAPLUS' ENTERED AT 08:38:36 ON 24 FEB 2009
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'MEDLINE' ENTERED AT 08:38:36 ON 24 FEB 2009

=> s (l1 or calmidazolium) and (fung? or parasit? or antifung? or antiparasit? or antimicrob? or microb?)
L2 60 (L1 OR CALMIDAZOLIUM) AND (FUNG? OR PARASIT? OR ANTIFUNG? OR ANTIPARASIT? OR ANTIMICROB? OR MICROB?)

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L3 56 L2 AND PY<=2004

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 41 DUP REM L3 (15 DUPLICATES REMOVED)

=> d l4 ibib abs 1-41

L4 ANSWER 1 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:59027 CAPLUS
DOCUMENT NUMBER: 142:370502
TITLE: Calcium-mediated protein secretion potentiates motility in Toxoplasma gondii
AUTHOR(S): Wetzel, Dawn M.; Chen, Lea Ann; Ruiz, Felix A.; Moreno, Silvia N. J.; Sibley, L. David
CORPORATE SOURCE: Department of Molecular Microbiology, Washington University School of Medicine, St Louis, MO, 63110, USA
SOURCE: Journal of Cell Science (2004), 117(24), 5739-5748
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apicomplexans such as Toxoplasma gondii actively invade host cells using a unique parasite-dependent mechanism termed gliding motility. Calcium-mediated protein secretion by the parasite has been implicated in this process, but the precise role of calcium signaling in motility remains unclear. Here we used calmidazolium as a tool to stimulate intracellular calcium fluxes and found that this drug led to enhanced motility by T. gondii. Treatment with calmidazolium increased the duration of gliding and resulted in trails that were twice as long as those formed by control parasites. Calmidazolium also increased microneme secretion by T. gondii, and studies with a deletion mutant of the accessory protein m2AP specifically implicated that adhesin MIC2 was important for gliding. The effects of calmidazolium on gliding and secretion were due to increased release of calcium from intracellular stores and calcium influx from the extracellular milieu. In addition, we demonstrate that calmidazolium -stimulated increases in intracellular calcium were highly dynamic, and that rapid fluxes in calcium levels were associated with parasite motility. Our studies suggest that oscillations in intracellular calcium levels may regulate microneme secretion and control gliding motility in T. gondii.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2004618582 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15591836
TITLE: Influence of calcium ion on host cell invasion and intracellular replication by Toxoplasma gondii.
AUTHOR: Song Hyun-Ouk; Ahn Myoung-Hee; Ryu Jae-Sook; Min Duk-Young; Joo Kyoung-Hwan; Lee Young-Ha
CORPORATE SOURCE: Department of Parasitology and Institute of Biomedical Science, Hanyang University College of Medicine, Seoul 133-791, Korea.
SOURCE: The Korean journal of parasitology, (2004 Dec) Vol. 42, No. 4, pp. 185-93.
Journal code: 9435800. ISSN: 0023-4001.
PUB. COUNTRY: Korea (South)
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20 Dec 2004
Last Updated on STN: 13 Jan 2005
Entered Medline: 12 Jan 2005

AB Toxoplasma gondii is an obligate intracellular protozoan parasite , which invades a wide range of hosts including humans. The exact mechanisms involved in its invasion are not fully understood. This study focused on the roles of Ca2+ in host cell invasion and in T. gondii replication. We examined the invasion and replication of T. gondii pretreated with several calcium modulators, the conoid extrusion of tachyzoites. Calmodulin localization in T. gondii were observed using the immunogold method, and Ca2+ levels in tachyzoites by confocal microscopy. In light microscopic observation, tachyzoites co-treated with A23187 and EGTA showed that host cell invasion and intracellular replication were decreased. The invasion of tachyzoites was slightly inhibited by the Ca2+ channel blockers, bepridil and verapamil, and by the calmodulin antagonist, calmidazolium. We observed that calcium saline containing A23187 induced the extrusion of tachyzoite conoid. By immunoelectron microscopy, gold particles bound to anti-calmodulin or anti-actin mAb, were found to be localized on the anterior portion of tachyzoites. Remarkably reduced intracellular Ca2+ was observed in tachyzoites treated with BAPTA/AM by confocal microscopy. These results suggest that host cell invasion and the intracellular replication of T. gondii tachyzoites are inhibited by the calcium ionophore, A23187, and by the extracellular calcium chelator, EGTA.

L4 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:218830 CAPLUS
DOCUMENT NUMBER: 139:111113
TITLE: Small ligands modulating the activity of mammalian adenylyl cyclases: A novel mode of inhibition by calmidazolium
AUTHOR(S): Haunso, Anders; Simpson, James; Antoni, Ferenc A.
CORPORATE SOURCE: Department of Neuroscience, University of Edinburgh, Edinburgh, UK
SOURCE: Molecular Pharmacology (2003), 63(3), 624-631
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mol. cloning of membrane-spanning mammalian adenylyl cyclases (ACs) has led to the discovery of nine different isotypes, making ACs potentially

useful therapeutic targets. This study investigated the mechanism by which fungicidal nitroimidazole compds. modulate AC activity. Current evidence indicates that biol. control of AC activity occurs through the cytosolic domains. Hence, full-length ACII, ACIX, and recombinant fusion proteins composed of the cytoplasmic loops of human ACIX or the first and second cytoplasmic loops of rat ACV and ACII, resp., were expressed in human embryonic kidney 293 cells. The AC activities of the resp. proteins were characterized, and their modulation by nitroimidazoles was investigated. Calmidazolium inhibited the activities of both full-length ACs and soluble fusion proteins (IC50, .apprx.10 μM). Inhibition of ACIX by calmidazolium was mediated by direct interaction with the catalytic core in a noncompetitive fashion. ACIX was essentially insensitive to 2'-deoxyadenosine 3'-monophosphate, a known blocker of AC activity. The ACV-ACII fusion protein was inhibited by calmidazolium (IC50, .apprx.20 μM) as well as by 2'-deoxyadenosine 3'-AMP (IC50, .apprx.2 μM), in a manner indicating independent mechanisms of action. Taken together, the data demonstrate that ACIX is insensitive to adenosine analogs and that calmidazolium inhibits AC activity by a novel, noncompetitive mechanism.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2003:584892 CAPLUS

DOCUMENT NUMBER: 140:56123

TITLE: Functional and genetic characterization of calmodulin from the dimorphic and pathogenic fungus Paracoccidioides brasiliensis

AUTHOR(S): de Carvalho, Maria Jose A.; Amorim Jesuino, Rosalia S.; Daher, Bruno S.; Silva-Pereira, Ildinete; de Freitas, Sonia M.; Soares, Celia M. A.; Felipe, M. Sueli S.

CORPORATE SOURCE: Lab. de Biologia Molecular, Universidade de Brasilia, Brasilia, 70910-900, Brazil

SOURCE: Fungal Genetics and Biology (2003), 39(3), 204-210
CODEN: FGBIFV; ISSN: 1087-1845

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Calmodulin (CaM) modulates intracellular calcium signalling and acts on several metabolic pathways and gene expression regulation in many eukaryotic organisms including human fungal pathogens, such as Candida albicans and Histoplasma capsulatum. The temperature-dependent dimorphic fungus Paracoccidioides brasiliensis is the etiol. agent of paracoccidioidomycosis (PCM). The mycelium (M) to yeast (Y) transition has been shown to be essential for establishment of the infection, although the precise mol. mechanisms of dimorphism in P. brasiliensis are still unknown. In this work, several inhibitory drugs of the Ca2+/calmodulin signalling pathway were tested to verify the role of this pathway in the cellular differentiation process of P. brasiliensis. EGTA and the drugs calmidazolium (R24571), trifluoperazine (TFP), and W7 were able to inhibit the M-Y transition. We have cloned and characterized the calmodulin gene from P. brasiliensis, which comprises 924 nucleotides and five introns that are in a conserved position among calmodulin genes.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:309776 CAPLUS

DOCUMENT NUMBER: 136:319388
TITLE: Methods and compositions for enhancing the immunostimulatory effect of interleukin-12
INVENTOR(S): Trinchieri, Giorgio; Lee, William M. F.; Koblish, Holly
PATENT ASSIGNEE(S): The Wistar Institute of Anatomy and Biology, USA; The Trustees of the University of Pennsylvania
SOURCE: U.S., 19 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 6375944	B1	20020423	US 1999-395038		19990913	<--
US 20020081277	A1	20020627	US 2002-79068		20020220	<--
PRIORITY APPLN. INFO.:			US 1998-101698P	P	19980925	
			US 1999-395038	A3	19990913	

AB The invention discloses a method for enhancing the therapeutic and adjuvant use of IL-12 by reducing unwanted transient immunosuppression caused by IL-12 or by high doses thereof by co-administering IL-12 with an effective amount of an agent that inhibits or neutralizes nitric oxide (NO) in vivo. This enhanced vaccine therapy involves co-administering the IL-12 adjuvant, a selected vaccine antigen and the NO inhibiting/neutralizing agent. Addnl., the toxicity of IL-12 treatment may be reduced by co-administering IL-12 with an effective amount of the NO inhibiting or neutralizing agent. A therapeutic composition characterized by reduced toxicity in mammals contains IL-12, preferably a low dose thereof, and an NO inhibiting or neutralizing agent in a pharmaceutically acceptable carrier. A vaccine composition contains an effective adjuvant amount of IL-12, an effective amount of an NO inhibiting or neutralizing agent, and an effective protective amount of a vaccine antigen in a pharmaceutically acceptable carrier.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2002:351458 CAPLUS
DOCUMENT NUMBER: 137:75697
TITLE: Inhibition of Ca2+/calmodulin-dependent protein kinase blocks morphological differentiation of Plasmodium gallinaceum zygotes to ookinetes
AUTHOR(S): Silva-Neto, Mario A. C.; Atella, Georgia C.; Shahabuddin, Mohammed
CORPORATE SOURCE: Laboratory of Malaria and Vector Research, NIAID, National Institutes of Health, Bethesda, MD, 20892-0425, USA
SOURCE: Journal of Biological Chemistry (2002), 277(16), 14085-14091
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Once ingested by mosquitoes, malaria parasites undergo complex cellular changes. These include zygote formation, transformation of zygote to ookinete, and differentiation from ookinete to oocyst. Within the oocyst, the parasite multiplies into numerous sporozoites. Modulators of intracellular calcium homeostasis A23187, MAPTAM, and TMB-8

blocked ookinete development as did the calmodulin (CaM) antagonists W-7 and calmidazolium. Ca2+/CaM-dependent protein kinase inhibitor KN-93 also blocked zygote elongation, while its ineffective analog KN-92 did not have such effect. In vitro both zygote and ookinete exts. efficiently phosphorylated autocamtide-2, a classic CaM kinase substrate, which could be blocked by calmodulin antagonists W-7 and calmidazolium and CaM kinase inhibitor KN-93. These results demonstrated the presence of calmodulin-dependent CaM kinase activity in the parasite. KN-93-treated parasites, however, expressed the ookinete-specific enzyme chitinase and the ookinete surface antigen Pgs28 normally, suggesting that the morphol. untransformed parasites are biochem. mature ookinetes. In mosquitoes, KN-93-treated parasites did not develop as oocysts, while KN-92-treated parasites produced similar nos. of oocysts as controls. These data suggested that in Plasmodium gallinaceum morphol. development of zygote to ookinete, but not its biochem. maturation, relies on Ca2+/CaM-dependent protein kinase activity and demonstrated that the morphol. differentiation is essential for the further development of the parasite in infected blood-fed mosquitoes.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:744869 CAPLUS

DOCUMENT NUMBER: 138:297010

TITLE: A high throughput screen for inhibitors of fungal cell wall synthesis

AUTHOR(S): Evans, Jonathan M.; Zaworski, Phillip G.; Parker, Christian N.

CORPORATE SOURCE: Discovery Technologies, Pharmacia Corp., Kalamazoo, MI, USA

SOURCE: Journal of Biomolecular Screening (2002), 7(4), 359-366
CODEN: JBISF3; ISSN: 1087-0571

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fungal cell wall synthesis is essential for viability, requiring the activity of genes involved in environmental sensing, precursor synthesis, transport, secretion, and assembly. This multitude of potential targets, the availability of known agents targeting this pathway, and the unique nature of fungal cell wall synthesis make this pathway an appealing target for drug discovery. Here the authors describe the adaptation of an assay monitoring cell wall synthesis for high-throughput screening. The assay requires fungal cell growth, in the presence of the test compound, for 3 h before the cells are subjected to osmotic shock in the presence of a dye that stains DNA. Miniaturization of the assay to a 384-well plate format and removing a mech. transfer led to subtle changes in the assay characteristics. Validation of the assay with a library of known pharmacol. active agents has identified a number of different classes of compds. that are active in this assay, causing aberrant cell wall morphol. and in many cases the inhibition of fungal cell growth.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2002:810219 CAPLUS

DOCUMENT NUMBER: 138:52595

TITLE: Antifungal activity in Saccharomyces cerevisiae is modulated by calcium signalling

AUTHOR(S): Edlind, Thomas; Smith, Lamar; Henry, Karl; Katiyar,

Santosh; Nickels, Joseph
CORPORATE SOURCE: Departments of Microbiology and Immunology, MCP Hahnemann School of Medicine, Philadelphia, PA, 19129, USA
SOURCE: Molecular Microbiology (2002), 46(1), 257-268
CODEN: MOMIEE; ISSN: 0950-382X
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The most important group of antifungals is the azoles (e.g. miconazole), which act by inhibiting lanosterol demethylase in the sterol biosynthesis pathway. Azole activity can be modulated through structural changes in lanosterol demethylase, altered expression of its gene ERG11, alterations in other sterol biosynthesis enzymes or altered expression of multi-drug transporters. We present evidence that azole activity vs. Saccharomyces cerevisiae is also modulated by Ca2+-regulated signalling. (i) Azole activity was reduced by the addition of Ca2+. Conversely, azole activity was enhanced by the addition of Ca2+ chelator EGTA. (ii) Three structurally distinct inhibitors (fluphenazine, calmidazolium and a W-7 analog) of the Ca2+-binding regulatory protein calmodulin enhanced azole activity. (iii) Two structurally distinct inhibitors (cyclosporin and FK506) of the Ca2+-calmodulin-regulated phosphatase calcineurin enhanced azole activity. (iv) Strains in which the Ca2+ binding sites of calmodulin were eliminated and strains in which the calcineurin subunit genes were disrupted demonstrated enhanced azole sensitivity; conversely, a mutant with constitutively activated calcineurin phosphatase demonstrated decreased azole sensitivity. (v) CRZ1/TCN1 encodes a transcription factor regulated by calcineurin phosphatase; its disruption enhanced azole sensitivity, whereas its over-expression decreased azole sensitivity. All the above treatments had comparable effects on the activity of terbinafine, an inhibitor of squalene epoxidase within the sterol biosynthesis pathway, but had little or no effect on the activity of drugs with unrelated targets. (vi) Treatment of S. cerevisiae with azole or terbinafine resulted in transcriptional upregulation of genes FKS2 and PMR1 known to be Ca2+ regulated. A model to explain the role of Ca2+-regulated signalling in azole/terbinafine tolerance is proposed.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2002364760 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12106602
TITLE: Identification of a signaling cascade for interleukin-8 production by Helicobacter pylori in human gastric epithelial cells.
AUTHOR: Nozawa Yoshihisa; Nishihara Katsushi; Peek Richard M; Nakano Motoko; Uji Tatsuya; Ajioka Hirofusa; Matsuura Naosuke; Miyake Hidekazu
CORPORATE SOURCE: Pharmacology Research Laboratory, Taiho Pharmaceutical Co., Ltd., 224-2 Ebisuno, Hiraishi, Kawauchi-cho, Tokushima, Japan.. y-nozawa@taiho.co.jp
SOURCE: Biochemical pharmacology, (2002 Jul 1) Vol. 64, No. 1, pp. 21-30.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 12 Jul 2002

Last Updated on STN: 8 Aug 2002
Entered Medline: 7 Aug 2002

AB Infecting gastric epithelial cells with Helicobacter pylori (H. pylori) has been shown to induce interleukin-8 (IL-8) production, but the signal transduction mechanism leading to IL-8 production is not defined clearly. In the present study, we investigated the molecular mechanism responsible for H. pylori-induced IL-8 release in human gastric epithelial cells. IL-8 levels in culture supernatants were determined by an enzyme linked-immunosorbent assay. Extracellular signal-regulated kinase (ERK) activity was tested using an in vitro kinase assay, which measured the incorporation of [gamma-33P]ATP into a synthetic peptide that is a specific ERK substrate. ERK phosphorylation and IkappaBalpha degradation by H. pylori infection were assessed by western blotting. In MKN45 cells, H. pylori-induced IL-8 release in a time-dependent manner. This IL-8 release was abolished by treatment with intracellular Ca2+ chelators (BAPTA-AM and TMB-8) but not by EGTA or nifedipine. The Ca2+ ionophore A23187 also induced IL-8 release to an extent similar to that of H. pylori infection. Calmodulin inhibitors (W7 and calmidazolium) and tyrosine kinase inhibitors (genistein and ST638) completely blocked IL-8 release by H. pylori and A23187. PD98059, an ERK pathway inhibitor, completely abolished H. pylori-induced IL-8 release. Moreover, BAPTA-AM, calmidazolium, and genistein, but not nifedipine, suppressed the ERK activation induced by H. pylori infection. PD98059 as well as MG132, an NF-kappaB pathway inhibitor, blocked both IL-8 production and degradation of IkappaBalpha induced by H. pylori infection, whereas only PD98059 inhibited ERK activity in response to H. pylori. There was no significant difference between IL-8 production induced by the cagA positive wild-type strain and the cagA negative isogenic mutant strain of H. pylori; therefore, CagA is not involved in the IL-8 production pathway. H. pylori-induced IL-8 production is dominantly regulated by Ca2+/calmodulin signaling, and ERK plays an important role in signal transmission for the efficient activation of H. pylori-induced NF-kappaB activity, resulting in IL-8 production.

L4 ANSWER 10 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2001:211795 CAPLUS
DOCUMENT NUMBER: 135:269854
TITLE: Structure, expression, and functional analysis of the gene coding for calmodulin in the chytridiomycete Blastocladiella emersonii
AUTHOR(S): Simao, Rita de Cassia Garcia; Gomes, Suely Lopes
CORPORATE SOURCE: Departmento de Bioquimica, Instituto de Quimica, Universidade de Sao Paulo, Sao Paulo, 05508-900, Brazil
SOURCE: Journal of Bacteriology (2001), 183(7), 2280-2288
CODEN: JOBAAY; ISSN: 0021-9193
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The single calmodulin (CaM) gene and the corresponding cDNA of the chytridiomycete Blastocladiella emersonii were isolated and characterized. The CaM gene is interrupted by three introns and transcribed in a single 0.7-kb mRNA species encoding a predicted protein 91% identical to human CaM. B. emersonii CaM has been expressed in Escherichia coli as a fusion protein with gluthatione S-transferase (GST) and purified by affinity chromatog. and cleavage from the GST portion using a site-specific protease. In the presence of Ca2+, B. emersonii CaM exhibited a shift in apparent mol. mass similar to that observed with bovine CaM and was able to activate the autophosphorylation of CaM-dependent protein kinase II (CaMKII) from rat brain. CaM expression is developmentally regulated in B. emersonii, with CaM mRNA and protein concns. increasing during

sporulation to maximum levels observed just prior to the release of the zoospores into the medium. Both CaM protein and mRNA levels decrease drastically at the zoospore stage, increasing again during germination. The CaM antagonists compound 48/80, calmidazolium, and W7 were shown to completely inhibit B. emersonii sporulation when added to the cultures at least 120, 150, and 180 min after induction, resp. All these drugs also inhibited growth and zoospore production in this fungus. The Ca2+ channel blocker TMB-8 and the CaMKII inhibitor KN93 completely inhibited sporulation if added up to 60 min after induction of this stage, but only KN93 affected fungal growth. The data presented suggest that the Ca2+-CaM complex and CaMKII play an important role during growth and sporulation in B. emersonii.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:563206 CAPLUS
DOCUMENT NUMBER: 135:315687
TITLE: Detection of calmodulin-binding proteins and calmodulin-dependent phosphorylation linked to calmodulin-dependent chemotaxis to folic acid and cAMP in Dictyostelium
AUTHOR(S): Gauthier, M. L.; O'Day, D. H.
CORPORATE SOURCE: Department of Zoology, University of Toronto at Mississauga, Mississauga, ON, L5L 1C6, Can.
SOURCE: Cellular Signalling (2001), 13(8), 575-584
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Calmodulin (CaM) antagonists, trifluoperazine (TFP) or calmidazolium (R24571), dose-dependently inhibited cAMP and folic acid (FA) chemotaxis in Dictyostelium. Developing, starved, and refed cells were compared to determine if certain CaM-binding proteins (CaMBPs) and CaM-dependent phosphorylation events could be identified as potential downstream effectors. Recombinant CaM ([35S]VU-1-CaM) gel overlays coupled with cell fractionation revealed at least three dozen Ca2+-dependent and around 12 Ca2+-independent CaMBPs in Dictyostelium. The CaMBPs associated with early development were also found in exptl. starved cells (cAMP chemotaxis), but were different for the CaMBP population linked to growth-phase cells (FA chemotaxis). Probing Western blots with phosphoserine antibodies revealed several phosphoprotein bands that displayed increases when cAMP-responsive cells were treated with TFP. In FA-responsive cells, several but distinct phosphoproteins decreased when treated with TFP. These data show that unique CaMBPs are present in growing, FA-chemosensitive cells vs. starved cAMP-chemoresponsive cells that may be important for mediating CaM-dependent events during chemotaxis.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2001:186750 CAPLUS
DOCUMENT NUMBER: 134:350376
TITLE: Glutamate decarboxylase activity in Trichoderma viride conidia and developing mycelia
AUTHOR(S): Strigacova, Jana; Chovanec, Peter; Liptaj, Tibor; Hudecova, Daniela; Tursky, Timotej; Simkovic, Martin; Varecka, L'udovit
CORPORATE SOURCE: Department of Biochemistry and Microbiology, Slovak University of Technology, Bratislava, 81237, Slovakia
SOURCE: Archives of Microbiology (2001), 175(1),

32-40
CODEN: AMICCW; ISSN: 0302-8933
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamic acid decarboxylase (GAD) activity was measured in homogenates of conidia and both submerged and aerial mycelia of Trichoderma viride. The GAD activity in conidia had a temperature optimum at 30°C and a pH optimum at pH 4. GAD was stimulated by EDTA (2 mM) and was insensitive to treatment with calmodulin antagonists calmidazolium (10 μM) or phenothiazine neuroleptics (60 μM). Cyclosporin A (up to 300 μM) partially inhibited GAD in the homogenate, but not in the supernatant obtained after centrifuging the homogenate. Attempts to release GAD activity from the homogenate using high ionic strength, detergents, or urea failed. Freezing-thawing led to the partial increase of activity in the conidial homogenate. These results indicate that GAD is a membrane-bound enzyme. The highest specific activity of GAD was present in the mitochondrial/vacuolar organellar fraction. Germination of conidia in the submerged culture led to a temporary decrease in GAD activity. After prolonged cultivation, the activity displayed quasi-oscillatory changes. The stationary state was characterized by a high GAD activity. The presence of γ-aminobutyric acid in the submerged mycelia was demonstrated. In surface culture in the dark, GAD activity increased in a monophasic manner until conidia formation. The illumination of dark-cultivated mycelia by a white-light pulse caused a dramatic increase in GAD activity. Light-induced changes were not observed in mutants with delayed onset of conidiation. In the dark or upon illumination by light pulse, the increase of GAD activity preceded the appearance of conidia. Thus, GAD activity in T. viride is closely associated with its developmental status and may represent a link between differentiation events and energy metabolism
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2000315717 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10856426
TITLE: Effect of calmidazolium analogs on calcium influx in HL-60 cells.
AUTHOR: Harper J L; Daly J W
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Biochemical pharmacology, (2000 Aug 1) Vol. 60, No. 3, pp. 317-24.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20 Jul 2000
Last Updated on STN: 20 Jul 2000
Entered Medline: 13 Jul 2000
AB The structure-activity relationships of calmidazolium analogs with respect to intracellular calcium levels were investigated in HL-60 cells. Quaternized derivatives of miconazole and clotrimazole, known inhibitors of store-operated calcium (SOC) channels, were synthesized. The quaternary N-methyl derivatives of miconazole (3) and clotrimazole (6) had no effect on intracellular calcium levels, alone or after elevation of calcium induced by ATP. Calmidazolium alone induced a large increase in intracellular calcium levels in HL-60 cells (EC(50) 3 microM).

Similar effects were observed for miconazole derivatives 1 (EC(50) 15 microM) and 2 (EC(50) 10 microM), wherein the diphenylmethyl group in calmidazolium was replaced by a 3,5-difluorobenzyl or cyclohexylmethyl group, respectively. The analogous clotrimazole derivatives 4 and 5 had no effect on intracellular calcium levels. The elevation of calcium levels by calmidazolium, 1, and 2 appears to be comprised of a calcium release component from inositol trisphosphate (IP(3))-sensitive stores followed by a large calcium influx component. Calcium influx was greater than that normally observed due to depletion of IP(3)-sensitive calcium stores and activation of SOC channels. In addition, only a small component of the calmidazolium-elicited influx was inhibited by the SOC channel blocker miconazole. Thus, certain quaternized imidazoles substituted with large residues at both nitrogens of the imidazole ring caused both release and influx of calcium, the latter in part through SOC channels but mainly through an undefined cationic channel. Quaternized imidazoles, unlike the parent nonquaternary imidazole miconazole, did not block SOC channels. Inhibitory effects on calmodulin-activated phosphodiesterase did not correlate with effects on calcium release and influx.

L4 ANSWER 14 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1999:668947 CAPLUS
DOCUMENT NUMBER: 132:146198
TITLE: Amphotericin B-induced interleukin-1β expression in human monocytic cells is calcium and calmodulin dependent
AUTHOR(S): Rogers, P. David; Kramer, Robert E.; Chapman, Stanley W.; Cleary, John D.
CORPORATE SOURCE: Departments of Clinical Pharmacy Practice, University of Mississippi Medical Center, Jackson, MS, 39216-4505, USA
SOURCE: Journal of Infectious Diseases (1999), 180(4), 1259-1266
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amphotericin B remains the agent of choice for treatment of severe fungal infections. Its use is hindered by adverse effects, including infusion-related fever, chills, and hypotension, as well as nephrotoxicity with secondary anemia, hypokalemia, and hypomagnesemia. Amphotericin B-induced transcription and expression of interleukin (IL)-1β by human monocytes is believed to be involved in mediating infusion-related adverse effects. It is shown here that agents that increase intracellular calcium [Ca++]i (A23187 and thapsigargin) in human monocytic cells also induce IL-1β expression. Furthermore, amphotericin B-induced IL-1β expression is attenuated by the calmodulin antagonist calmidazolium. Amphotericin B 5.41 μM increases [Ca++]i by up to 300 nM in these cells. In the presence of a nominal calcium buffer or EGTA, amphotericin B-induced IL-1β expression is attenuated. Thus, amphotericin B acts as an ionophore to increase [Ca++]i and activates calmodulin-mediated expression of IL-1β in human monocytes.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:805755 CAPLUS
DOCUMENT NUMBER: 128:70786
ORIGINAL REFERENCE NO.: 128:13691a,13694a
TITLE: Glycine transporter-transfected cells and uses thereof
INVENTOR(S): Ognyanov, Vassil Iliya; Borden, Laurence; Bell,

Stanley Charles; Zhang, Jing
PATENT ASSIGNEE(S): Trophix Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9745446	A1	19971204	WO 1997-US9347	19970529 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5824486	A	19981020	US 1996-655836	19960531 <--
CA 2254835	A1	19971204	CA 1997-2254835	19970529 <--
CA 2254835	C	20070710		
AU 9732232	A	19980105	AU 1997-32232	19970529 <--
AU 735905	B2	20010719		
EP 954527	A1	19991110	EP 1997-927880	19970529 <--
EP 954527	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000513213	T	20001010	JP 1997-543002	19970529 <--
AT 286065	T	20050115	AT 1997-927880	19970529
US 5968823	A	19991019	US 1998-20753	19980209 <--

PRIORITY APPLN. INFO.: US 1996-655836 A 19960531
WO 1997-US9347 W 19970529

AB The present invention relates to materials and methods for the identification of agents that regulate glycine transport in or out of cells, particularly in or out of neuronal and neuronal-associated cells. Such materials include non-mammalian cells having transfected therein a glycine transporter. The methods relate to the manipulation of such cells such that agents are identified that cause intake or outflow of glycine with respect to a given glycine transporter.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1997:588003 CAPLUS
DOCUMENT NUMBER: 127:245346
ORIGINAL REFERENCE NO.: 127:47851a,47854a
TITLE: Involvement of calcium and calmodulin in Toxoplasma gondii tachyzoite invasion
AUTHOR(S): Pezzella, Nathalie; Bouchot, Andre; Bonhomme, Annie; Pingret, Laure; Klein, Christophe; Burlet, Henriette; Balossier, Gerard; Bonhomme, Pierre; Pinon, Jean Michel
CORPORATE SOURCE: Laboratoire Parasitologie, Univ. Reims Champagne-Ardenne, Reims, F-51092, Fr.
SOURCE: European Journal of Cell Biology (1997), 74(1), 92-101
CODEN: EJCBDN; ISSN: 0171-9335
PUBLISHER: Wissenschaftliche Verlagsgesellschaft
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The tachyzoite of T. gondii must successfully invade a host cell before it

can replicate. Depletion of the Ca2+ in the external medium (EGTA) reduced tachyzoite invasion, suggesting that the initial tachyzoite-host cell interaction is Ca2+ dependent. The interaction of tachyzoites with host cells was also inhibited by Ca2+ channel blockers (verapamil) and calmodulin antagonists (trifluoperazine, calmidazolium). The calmodulin concentrated at the apical end of the tachyzoite could be involved in cytoskeleton movement and conoid extrusion. Invasion also depends on changes in tachyzoite cytosolic calcium. Depletion of Ca2+ with A23187+EGTA and release of Ca2+ from intratachyzoite pools (nuclear and perinuclear areas) inhibited invasion. In contrast, Ca-ionophore and thapsigargin which increase host cell cytosolic Ca2+, decreased tachyzoite invasion. It was suggested that the effect of the drug is different from the localized Ca2+ signal that is produced after parasite attachment to its host cell receptors and leads to its internalization into the host cell.

L4 ANSWER 17 OF 41 MEDLINE on STN
ACCESSION NUMBER: 1996235207 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8645223
TITLE: KS-505a, an isoform-selective inhibitor of calmodulin-dependent cyclic nucleotide phosphodiesterase.
AUTHOR: Ichimura M; Eiki R; Osawa K; Nakanishi S; Kase H
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Kyowa Hakko Co., Ltd., Shizuoka, Japan.
SOURCE: The Biochemical journal, (1996 May 15) Vol. 316 (Pt 1), pp. 311-6.
Journal code: 2984726R. ISSN: 0264-6021.
Report No.: NLM-PMC1217340.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 26 Jul 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Jul 1996

AB The effects of KS-505a, a novel microbial metabolite, on the activity of calmodulin-dependent cyclic nucleotide phosphodiesterase (CaM-PDE) were investigated. (1) KS-505a potently inhibited the purified 61 kDa isoenzyme of CaM-PDE from bovine brain and required much higher doses to inhibit the purified 59 kDa isoenzyme of CaM-PDE from bovine heart. The inhibition of both isoenzymes was observed only in the presence of calcium-activated calmodulin (Ca2+/CaM). The IC50 values for the 61 and 59 kDa isoenzymes were 0.17 and 13 microM respectively with 20 microM cAMP as a substrate. (2) Kinetic analysis indicated that the inhibitory mode of KS-505a for the 61 kDa isoenzyme was competitive with respect to Ca2+/CaM; the K1 for KS-505a was 0.089 microM. The inhibition was not competitive with respect to the substrates cAMP or cGMP. (3) KS-505a did not interfere with the interaction between Ca2+/CaM and n-phenyl1-naphthylamine, a hydrophobic fluorescent probe, nor was it adsorbed to CaM-conjugated gels in the presence of Ca2+, thereby indicating that KS-505a does not bind to Ca2+/CaM. (4) Trypsin-activated 61 kDa isoenzyme, which lacked the Ca2+/CaM-binding domain, was not inhibited by KS-505a at less than micromolar concentrations. Taken together, these results suggest that KS-505a apparently bound to a site in the Ca2+/CaM-binding domain of the 61 kDa isoenzyme and selectively inhibited Ca2+/CaM-activated 61 kDa isoenzyme activity. (5) In rat hippocampal slices, KS-505a at 10 micronM increased the intracellular cAMP concentration to approximately three times the basal level, whereas in rat striatal slices it had no effect on the cAMP concentration at

concentrations of 1.0-10 microM, suggesting that each CaM-PDE isoenzyme functions differentially in these regions. These results demonstrate that KS-505a is a highly potent selective inhibitor both in vitro and in vivo and distinguishes between subfamily members within the CaM-PDE family.

L4 ANSWER 18 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1996:517577 CAPLUS
DOCUMENT NUMBER: 125:216666
ORIGINAL REFERENCE NO.: 125:40395a,40398a
TITLE: Trypanosoma cruzi: Involvement of intracellular calcium in multiplication and differentiation
AUTHOR(S): Lammel, Estela M.; Barbieri, Manuel A.; Wilkowsky, Silvina E.; Bertini, Francisco; Isola, Elvira L. D.
CORPORATE SOURCE: Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, 2155, Argent.
SOURCE: Experimental Parasitology (1996), 83(2), 240-249
CODEN: EXPAAA; ISSN: 0014-4894
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The possible role of intracellular Ca2+ level on T. cruzi differentiation was explored. The addition to epimastigotes of a Triatoma infestans intestinal homogenate, which that triggers off the differentiation to the infective metacyclic form, induced a sudden rise in [Ca2+]i from the basal value, 94 ± 28 to 584 ± 43 nmole/L. This increase was not affected by the presence of EGTA in the medium. Trypsin-treated intestinal homogenate did not alter the [Ca2+]i of epimastigotes. Calmodulin inhibitors (Calmidazolium, Trifluoperazine, and Chlorpromazine) blocked differentiation. Although the Ca ionophore ionomycin increased [Ca2+]i to 342 ± 29 nmole/L, it was unable to induce differentiation by itself. BAY K8644 and Methoxyverapamil (agonist and antagonist of Ca2+ channels, resp.) were unable to affect [Ca2+]i by themselves, or when added to stimulated parasites, and did not exert a stimulatory or inhibitory effect on morphogenesis. BAPTA/AM, a Ca2+ chelator, partially blocked the rise in [Ca2+]i and morphogenesis; this effect was reversed by ionomycin. The requirement of intracellular Ca2+ on epimastigote multiplication was also evaluated. The addition of EGTA to the culture medium led to a decrease in epimastigote multiplication till it practically ceased in the 6th passage. When such parasites were transferred to liver infusion tryptose medium they partially recovered the growth rate. Parasites from passages III, IV, and V in the Ca2+ -depleted medium maintained their basal [Ca2+]i, but when treated with the intestinal homogenate, the rise in [Ca2+]i was abrogated. Accordingly, the differentiation percentages of such parasites dropped significantly compared with controls.

L4 ANSWER 19 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1995:876642 CAPLUS
DOCUMENT NUMBER: 124:25274
ORIGINAL REFERENCE NO.: 124:4767a,4770a
TITLE: Mobilization of intrasporozoite Ca2+ is essential for Theileria parva sporozoite invasion of bovine lymphocytes
AUTHOR(S): Shaw, Michael K.
CORPORATE SOURCE: International Laboratory Research Animal Diseases (ILRAD), Nairobi, Kenya
SOURCE: European Journal of Cell Biology (1995), 68(1), 78-87
CODEN: EJCBDN; ISSN: 0171-9335
PUBLISHER: Wissenschaftliche Verlagsgesellschaft
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The entry of Theileria parva sporozoites into bovine lymphocytes occurs rapidly and involves a defined series of events. In the present study, the role of calcium in sporozoite entry was examined Depletion of Ca2+ from the external medium had little effect on sporozoite entry suggesting that the initial sporozoite-host cell interaction is a Ca2+-independent process. Sporozoite entry could, however, be inhibited by a range of Ca2+ channel blockers (verapamil, nicardipine, diltiazem) and calmodulin antagonists (TPF, chlorpromazine, W7 and calmidazolium). Evidence is also presented that demonstrates that sporozoite entry is dependent on changes in sporozoite cytosolic Ca2+ caused by the release of Ca2+ from intrasporozoite stores. First, reagents that produced an influx of Ca2+ into the parasite (A23187) blocked entry. Second, depletion of intrasporozoite Ca2+ levels (10 μM A23187+1.0 mM EGTA) or an increase in the cytoplasmic buffering capacity of the sporozoite cytoplasm (by preloading sporozoites with MAPT/AM) inhibited invasion. Third, sporozoite entry was inhibited by TMB-8 which blocks the release of Ca2+ from intracellular stores. Lastly, treatment of sporozoites with the Ca2+-mobilizing agents thapsigargin and cyclopiazonic acid, but not InsP3, prevented sporozoite entry. In these cases, the premature release of intrasporozoite Ca2+ inhibited sporozoite binding to the host cell surface; sporozoites that bound became internalized at rates comparable to the controls. In contrast, treatment of lymphocytes with these reagents had no significant effect on sporozoite entry. Collectively, the mobilization of Ca2+ from intrasporozoite stores following sporozoite binding to the host cell surface is essential for successful parasite invasion.

L4 ANSWER 20 OF 41 MEDLINE on STN

ACCESSION NUMBER: 1995194813 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7888302
TITLE: Calmodulin function and calmodulin-binding proteins during autoactivation and spore germination in Dictyostelium discoideum.
AUTHOR: Lydan M A; Cotter D A; O'Day D H
CORPORATE SOURCE: University of Windsor, Department of Biological Sciences, Ontario, Canada.
SOURCE: Cellular signalling, (1994 Sep) Vol. 6, No. 7, pp. 751-62.
Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 27 Apr 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 20 Apr 1995

AB Dictyostelium discoideum spores can be activated to initiate germination either endogenously via a diffusible autoactivator, or exogenously via heat. Following activation, three successive stages of germination occur, the lag stage, spore swelling and amoebal emergence. A previous study [Lydan M. A. and Cotter D. A. (1994) FEBS Lett. 115, 137-142] has shown that spore swelling is dependent on the activity of calmodulin. In this study, the calmodulin antagonists trifluoperazine and calmidazolium inhibited autoactivation, but had no effect upon heat activation. These agents also inhibited amoebal emergence following either form of activation. The effects caused by the anti-calmodulin agents were specific to an inhibition of calmodulin function since agents which modulate the activity of protein kinase C had no effect upon spore germination. A calcium-dependent calmodulin-binding protein of about

64,000 M(r) may be associated with the process of autoactivation since it was only seen in those spores which respond to the autoactivator. Overall, this study provides evidence to show that calmodulin plays a regulatory role during autoactivation and amoebal emergence during spore germination in D. discoideum and provides evidence for the calmodulin-dependent mechanisms which mediate each of these phases of germination.

L4 ANSWER 21 OF 41 MEDLINE on STN
ACCESSION NUMBER: 1994257013 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8198606
TITLE: Stage-specific changes in protein phosphorylation during spore germination in Dictyostelium: role of calmodulin.
AUTHOR: Lydan M A; Cotter D A; O'Day D H
CORPORATE SOURCE: Department of Biological Sciences, University of Windsor, Ontario, Canada.
SOURCE: Biochemical and biophysical research communications, (1994 May 30) Vol. 201, No. 1, pp. 430-5.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 7 Jul 1994
Last Updated on STN: 7 Jul 1994
Entered Medline: 29 Jun 1994
AB Extensive protein phosphorylation occurs during all phases of spore germination in Dictyostelium discoideum. The developmental changes were prevented when germination was inhibited by inhibitors of calmodulin function. In addition, differences in patterns of phosphorylation were detected based upon the method of spore activation. Several phosphoproteins were lost in heat activated as compared to autoactivated spores. In spite of the fact that several aspects (i.e. autoactivation, emergence) are calmodulin-dependent, there was no evidence that calcium- or calmodulin-dependent protein kinase activity is present during any phase of spore germination. This suggests that other CaM-dependent processes mediate the diverse aspects of spore germination in D. discoideum.

L4 ANSWER 22 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 1994:599135 CAPLUS
DOCUMENT NUMBER: 121:199135
ORIGINAL REFERENCE NO.: 121:36079a,36082a
TITLE: Plasmodium falciparum calcium-dependent protein kinase phosphorylates proteins of the host erythrocytic membrane
AUTHOR(S): Zhao, Yi; Franklin, Richard M.; Kappes, Barbara
CORPORATE SOURCE: Department of Structural Biology, Biozentrum, University of Basel, Klingelbergstrasse 70, CH-4056, Basel, Switz.
SOURCE: Molecular and Biochemical Parasitology (1994), 66(2), 329-43
CODEN: MBIPDP; ISSN: 0166-6851
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The unusual Ca2+-dependent protein kinase from Plasmodium falciparum (I), of which the gene structure and expression in bacteria have been previously reported, was purified to homogeneity. Purified recombinant I had a native mol. weight of 62,000, was activated by Ca2+ (K0.5 = 15 μM) in the presence of Mg2+ or Mn2+, and could associate with 45Ca2+. The

activation by Ca2+ could be partially replaced by Mn2+, but not by Zn2+ or Mg2+. I preferentially phosphorylated casein and histone H1. The Km and Vmax values for Mg2+-ATP were 26 μM and 70 nmol min-1 mg-1, resp., with casein as substrate and 34 μM and 143 nmol min-1 mg-1, resp., with histone H1 as substrate. I underwent autophosphorylation on both serine and threonine residues. Calmodulin antagonists (calmidazolium, trifluoperazine, N-[6-aminohexyl]-5-chloro-1-naphthalene-sulfonamide, and ophiobolin A) inhibit I activation, but much higher concns. of the antagonists were needed than was required to inhibit calmodulin-mediated effects. I preferentially phosphorylated proteins of the host erythrocytic membrane in vitro but phosphorylated parasitic proteins only to a minor extent. The selectivity of the phosphorylation could be partially controlled by phosphatidylserine which was bound to some of the erythrocyte membrane proteins. Using a rabbit polyclonal antiserum against recombinant I, the enzyme was found to be mainly expressed in the ring and schizont stages, and mainly localized in the parasitic membrane-organelle fraction and partially localized on the erythrocyte membrane.

L4 ANSWER 23 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:449796 CAPLUS
DOCUMENT NUMBER: 121:49796
ORIGINAL REFERENCE NO.: 121:8747a,8750a
TITLE: Reversal of chloroquine resistance in falciparum malaria by some calcium channel inhibitors and optical isomers is independent of calcium channel blockade
AUTHOR(S): Ye, Zuguang; Dyke, Knox Van
CORPORATE SOURCE: Inst. Chin. Mater., China Acad. Tradi. Chinese Med., Beijing, 100700, Peop. Rep. China
SOURCE: Drug Chem. Toxicol. (1977) (1994), 17(2), 149-62
CODEN: DCTODJ; ISSN: 0148-0545
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Various types of calcium channel blockers verapamil, gallopamil, devapamil, diltiazem, and nifedipine and a calmodulin inhibitor R24571 were evaluated for reversal of chloroquine(CQ) resistance of Plasmodium falciparum in an in vitro system. The results demonstrated that some of the above Ca2+ antagonists such as verapamil, gallopamil, devapamil, and diltiazem were found to exert remarkable reversal activity of CQ resistance of the falciparum parasite in vitro, while the others like nifedipine and R24571 had no reversal properties of CQ resistance of the parasite. In addition, reversal activities of the CQ resistance by enantiomers of some calcium channel blockers(R-(+)-verapamil, R-(+)-gallopamil and R-(+)-devapamil), which do not bind to the calcium channel, were also observed in this study. The data strongly indicate that the mechanism of reversal of CQ resistance of falciparum malaria in vitro is independent of the calcium channel.

L4 ANSWER 24 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:211383 CAPLUS
DOCUMENT NUMBER: 120:211383
ORIGINAL REFERENCE NO.: 120:37337a,37340a
TITLE: Changes in protein kinase and protein phosphatase properties during the cycle of asparaginase activity in Leptosphaeria michotii
AUTHOR(S): Jerebzoff-Quintin, Simonne; Jerebzoff, Stephan
CORPORATE SOURCE: Lab. Biorythmes, Univ. Paul Sabatier, Toulouse, F-31062, Fr.
SOURCE: Physiologia Plantarum (1994), 90(1), 65-72
CODEN: PHPLAI; ISSN: 0031-9317
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Regulation of the cyclic activity of asparaginase (obtained as a purified protein complex) by a reversible auto-phosphorylation process has been previously reported in the fungus Leptosphaeria michotii (West) Sacc. In the present study, the protein complex was purified in the presence of either a mixture of 3 protein phosphatase inhibitors (fluoride, vanadate and molybdate) or EGTA, during the cycle of asparaginase activity, and the protein kinase and protein phosphatase activities characterized. At the phase of increasing asparaginase activity, a Ca2+/calmodulin-dependent kinase activity was identified by (a) its inhibition by calmidazolium, reversed by calmodulin, and its inhibition by EGTA, but not by poly(Glu/Tyr 4:1)n, dichloro-(ribofuranosyl)-benzimidazole or polylysine; (b) an increasing level of calmodulin bound to the complex, as estimated by ELISA. At the phase of decreasing asparaginase activity, the Ca2+-calmodulin-dependent kinase activity disappeared and a little calmodulin remained associated with the complex; phosphorylation of the complex was increased several-fold by 1 nM okadaic acid and 25 nM inhibitor-2, and was not affected by EGTA, indicating a protein phosphatase-2A-like activity. When asparaginase activity was low, a little calmodulin was bound to the complex. The kinase could phosphorylate casein and phosvitin, was inhibited by poly(Glu/Tyr 4:1)n, dichloro(ribofuranosyl)-benzimidazole and heparin, stimulated by polylysine and not affected by calmidazolium or EGTA, just as a casein kinase 2. A Ca2+-dependent but calmodulin-independent protein phosphatase activity, not affected by okadaic acid and inhibitor-2, was then identified. The authors postulate the presence in the complex of (a) only one protein kinase and one protein phosphatase, whose properties could change during the cycle of asparaginase activity; (b) two Ca2+-binding proteins: first, calmodulin, which could bind to Ca2+ and the casein kinase-2 form to give a Ca2+/calmodulin-dependent kinase, which could become Ca2+/calmodulin-independent following an autophosphorylation process; second, a protein homologous to calmodulin, able to bind to the protein phosphatase-2A catalytic subunit to give a protein phosphatase-2B catalytic subunit.

L4 ANSWER 25 OF 41 MEDLINE on STN

ACCESSION NUMBER: 1994172301 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8126432

TITLE: Calcium homeostasis, signalling and protein phosphorylation during calcium-induced conidiation in Penicillium notatum.

AUTHOR: Pitt D; Barnes J C

CORPORATE SOURCE: Department of Biological Sciences, University of Exeter, UK.

SOURCE: Journal of general microbiology, (1993 Dec) Vol. 139, No. 12, pp. 3053-63.
Journal code: 0375371. ISSN: 0022-1287.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199404

ENTRY DATE: Entered STN: 20 Apr 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 12 Apr 1994

AB Cytosolic free calcium concentration [Ca2+]c of protoplasts from Penicillium notatum was measured using the permeant acetoxy ester (quin-2-AM) of the calcium-chelating fluorescent dye quin-2. Low uptake of the ester occurred at pH 5.8-7.0 and its subsequent hydrolysis was low. Uptake was promoted by an external pH of 5.0 and significant hydrolysis to quin-2 achieved by adjustment of the internal pH to 7.2, which was near the optimum of the carboxylic esterases responsible for the hydrolysis.

Uptake of Ca2+ was biphasic with the average cell calcium concentration of protoplasts increasing from an initial value of 2 mumol to 50 mumol (kg cell water)-1, during attainment of the steady state after 30 min, at which time [Ca2+]c was unchanged at 20 nM but increased to 182 nM at 2-6 h exposure to 2.5 mM-Ca2+. Broadly similar changes in [Ca2+]c were found in protoplasts derived from mycelium samples exposed to Ca2+ over the same period of time. The location of Ca2+ was determined in subfractionated organelles and characterized using enzyme markers and electron microscopy. In 32 h mycelium preloaded with Ca2+ for 6 h, Ca2+ was located principally in the mitochondria with lower concentrations associated with the endoplasmic reticulum, Golgi, vacuoles and plasma membrane components. Calcium was not released by inositol 1,4,5-trisphosphate or the calcium ionophore A23187 from any subcellular fractions obtained from mycelium on Percoll gradients, nor from preparations of vacuoles or plasmalemma vesicles, except in the case of mitochondria where rapid release of the ion was achieved by the addition of 2-5 microM-A23187. The anti-calmodulin agent calmidazolium (R24571) greatly reduced sporulation when addition preceded that of Ca2+. Calcium-induced cultures showed massive novel protein phosphorylation 2 h after addition of the ion which was virtually eliminated by R24571, whilst 1 h and 4-6 h protein phosphorylations, which were also present to some degree in vegetative controls, were substantially reduced. Two-dimensional SDS-PAGE analysis of phosphoproteins confirmed that Ca(2+)-induced mycelium had enhanced capacity for calmodulin-mediated phosphorylation relative to corresponding vegetative cells and that complex differential changes in such phosphorylations occurred during Ca(2+)-induction of the sporulation process.

L4 ANSWER 26 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:101312 CAPLUS
DOCUMENT NUMBER: 120:101312
ORIGINAL REFERENCE NO.: 120:17831a,17834a
TITLE: Calcium homeostasis in Trypanosoma cruzi
AUTHOR(S): Docampo, Roberto
CORPORATE SOURCE: Dep. Vet. Pathobiol., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Biological Research (1993), 26(1-2), 189-196
CODEN: BESEEB; ISSN: 0716-9760
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 49 refs. The intracellular transport mechanisms involved in maintaining Ca2+ homeostasis in T. cruzi have been characterized by measuring Ca2+ transport in digitonin-permeabilized cells. Two intracellular calcium transport systems have been detected. Ca2+ uptake by the mitochondria occurs by an electrophoretic mechanism, is inhibited by antimycin A, FCCP, and ruthenium red, and is stimulated by respiratory substrates, phosphate and acetate. This pool has a high capacity and low affinity for Ca2+ and is able to buffer external Ca2+ at concns. in the range of 0.6-0.7 μM. Ca2+ uptake by the endoplasmic reticulum is inhibited by high concns. of vanadate and anticalmodulin agents and is stimulated by ATP. This pool has a low capacity and a high affinity for Ca2+ and is able to buffer external Ca2+ at concns. in the range of 0.05-1.0 μM. In addition, calmodulin has been purified from T. cruzi epimastigotes and shown to stimulate the homologous plasma membrane Ca2+-ATPase and cAMP phosphodiesterase. The gene encoding this protein has been cloned and sequenced and is shown to have a great homol. to mammalian calmodulin. The role of the plasma membrane of T. cruzi in the regulation of [Ca2+]i has been studied using fura 2-loaded epimastigotes or plasma membrane vesicles prepared from epimastigotes. Plasma membrane vesicles transport Ca2+ in the presence of Mg2+ and have a high affinity, vanadate-sensitive (Ca2+-Mg2+)-ATPase with an apparent Km for free Ca2+ of 0.3 μM. Ca2+-ATPase activity and Ca2+ transport are both stimulated by

endogenous calmodulin and inhibited by trifluoperazine and calmidazolium at concns. in the range in which they normally exert anti-calmodulin effects. These observations suggest that a Mg2+-dependent plasma membrane Ca2+ pump is present in these parasites. No convincing evidence, however, has been found of the presence of a Na+/Ca2+ exchanger or a calcium channel in the epimastigotes plasma membrane. There is some evidence for the involvement of Ca ions in the development of cell toxicity by several trypanocidal agents.

L4 ANSWER 27 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1992:567461 CAPLUS
DOCUMENT NUMBER: 117:167461
ORIGINAL REFERENCE NO.: 117:28855a,28858a
TITLE: Calcium involvement in dimorphism of Ophiostoma ulmi, the Dutch elm disease fungus, and characterization of calcium uptake by yeast cells and germ tubes
AUTHOR(S): Gadd, G. M.; Brunton, A. H.
CORPORATE SOURCE: Dep. Biol. Sci., Univ. Dundee, Dundee, DD1 4HN, UK
SOURCE: Journal of General Microbiology (1992), 138(8), 1561-71
CODEN: JGMIAN; ISSN: 0022-1287
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exogenous Ca2+, at concns. of ≤5 mM, induced partial germ tube formation in O. (=Ceratocystis) ulmi in media normally supporting growth in the yeast-like phase. The calmodulin inhibitors calmidazolium (R24571) and trifluoperazine (TFP) and the Ca2+ ionophore A23187 suppressed germ tube formation in germ tube-inducing medium without affecting yeast-like growth. R24571 was the most effective inhibitor, giving almost complete suppression at 3 μM. Addition of excess Ca2+ (≤5 mM) did not reverse the inhibitory action of R24571 and only .apprx.10% of yeast-like cells formed germ tubes on addition of Ca2+ in the presence of 20 μM TFP or 15 μM A23187. Intracellular cAMP increased on incubation with R24571 and A23187, possibly as a result of inhibition of the cAMP phosphodiesterase. The exogenous supply of the Ca-binding agents methylhydroxybenzoate (MHB) and EGTA also suppressed germ tube formation under inducing conditions. These results confirm an involvement of Ca2+ in the yeast-mycelium transition of O. ulmi. Yeast-like cells and germ tubes of O. ulmi exhibited metabolism-dependent Ca2+ uptake which was reduced in the absence of glucose, or by the presence of KCN, the ATPase inhibitors N,N'-dicyclohexylcarbodiimide (DCCD) and diethylstilboestrol (DES), and the protonophoric uncoupler DNP, indicating dependence on the electrochem. proton gradient across the plasma membrane generated by the H+-ATPase. Germ tubes exhibited greater sensitivity to inhibitors of Ca2+ uptake than yeast-like cells, while Ca2+ uptake was competitively inhibited by Mg2+, Mn2+ and Zn2+. R24571 and A23187 inhibited Ca2+ uptake by germ tubes, although TFP stimulated uptake in comparison to control cells. Ca2+ uptake by both cell types conformed to Michaelis-Menten kinetics at concns. below .apprx.200 μM but deviated strongly above this concentration Kinetic anal. of Ca2+ uptake by yeast-like cells and germ tubes, at Ca2+ concns. <100 μM, revealed that both cell types possessed Ca2+ transport systems of similar specificity, with Km values ranging between .apprx.15 and 25 μM, although germ tubes always exhibited greater Ca2+ uptake than yeast cells under similar exptl. conditions, possibly a consequence of increased vacuolar compartmentation.

L4 ANSWER 28 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1991:673661 CAPLUS
DOCUMENT NUMBER: 115:273661
ORIGINAL REFERENCE NO.: 115:46345a,46348a
TITLE: A calmodulin-activated calcium-magnesium ATPase is

involved in calcium transport by plasma membrane vesicles from Trypanosoma cruzi
AUTHOR(S): Benaim, Gustavo; Losada, Sandra; Gadelha, Eernanda R.; Docampo, Roberto
CORPORATE SOURCE: Dep. Vet. Pathobiol., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Biochemical Journal (1991), 280(3), 715-20
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB High-affinity Ca2+-activated ATPases that do not show any demonstrable dependence on Mg2+ have been reported in the plasma membranes of different trypanosomatids, and it has been suggested that these enzymes may have a role in Ca2+ transport by the plasma membrane and in the regulation of intracellular Ca2+ in these parasites. In this report, Ca2+ transport by T. cruzi plasma membrane vesicles was investigated using Arsenazo III as a Ca2+ indicator. These vesicles accumulated Ca2+ upon addition of ATP only when Mg2+ was present and released it in response to the Ca2+ ionophore A23187, but were insensitive to inositol 1,4,5-trisphosphate. Ca2+ transport was insensitive to antimycin A, oligomycin, and carbonyl cyanide p-trifluorophenylhydrazone, ruling out any mitochondrial contamination. Staurosporine and phorbol myristate acetate had no effect on this activity, while low concns. of vanadate (10 μM) completely inhibited it. In addition, a high-affinity vanadate-sensitive (Ca2+-Mg2+)-ATPase in the highly enriched plasma membrane fraction of T. cruzi is described. Kinetic studies indicated that the apparent Km for free Ca2+ was 0.3 μM. On the other hand, Ca2+-ATPase activity and Ca2+ transport were both stimulated by bovine brain calmodulin and by endogenous calmodulin purified from these cells. In addition, trifluoperazine and calmidazolium, at concns. in the range in which they normally exert anti-calmodulin effects, inhibited the calmodulin-stimulated Ca2+-ATPase activity. These observations support the notion that a Mg2+-dependent plasma membrane Ca2+ pump is present in these parasites.

L4 ANSWER 29 OF 41 MEDLINE on STN
ACCESSION NUMBER: 1992109672 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1837215
TITLE: A calmodulin-activated (Ca(2+)-Mg2+)-ATPase is involved in Ca2+ transport by plasma membrane vesicles from Trypanosoma cruzi.
AUTHOR: Benaim G; Losada S; Gadelha F R; Docampo R
CORPORATE SOURCE: Department of Veterinary Pathobiology, University of Illinois, Urbana 61801.
CONTRACT NUMBER: AI-23259 (United States NIAID NIH HHS)
SOURCE: The Biochemical journal, (1991 Dec 15) Vol. 280 (Pt 3), pp. 715-20.
Journal code: 2984726R. ISSN: 0264-6021.
Report No.: NLM-PMC1130512.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 2 Mar 1992
Last Updated on STN: 2 Mar 1992
Entered Medline: 11 Feb 1992

AB High-affinity Ca(2+)-activated ATPases that do not show any demonstrable dependence on Mg2+ have been reported in the plasma membranes of different

trypanosomatids, and it has been suggested [McLaughlin (1985) Mol. Biochem. Parasitol. 15, 189-201; Ghosh, Ray, Sarkar & Bhaduri (1990) J. Biol. Chemical 265, 11345-11351] that these enzymes may have a role in Ca2+ transport by the plasma membrane and in the regulation of intracellular Ca2+ in these parasites. In this report we investigated Ca2+ transport by Trypanosoma cruzi plasma membrane vesicles using Arsenazo III as a Ca2+ indicator. These vesicles accumulated Ca2+ upon addition of ATP only when Mg2+ was present and released it in response to the Ca2+ ionophore A23187, but were insensitive to inositol 1,4,5-trisphosphate. Ca2+ transport was insensitive to antimycin A, oligomycin and carbonyl cyanide p-trifluorophenylhydrazone, ruling out any mitochondrial contamination. Staurosporine and phorbol myristate acetate had no effect on this activity, while low concentrations of vanadate (10 microM) completely inhibited it. In addition, we describe a high-affinity vanadate-sensitive (Ca(2+)-Mg2+)-ATPase in the highly enriched plasma membrane fraction of T. cruzi. Kinetic studies indicated that the apparent Km for free Ca2+ was 0.3 microM. On the other hand, Ca(2+)-ATPase activity and Ca2+ transport were both stimulated by bovine brain calmodulin and by endogenous calmodulin purified from these cells. In addition, trifluoperazine and calmidazolium, at concentrations in the range in which they normally exert anti-calmodulin effects, inhibited the calmodulin-stimulated Ca(2+)-ATPase activity. These observations support the notion that a Mg(2+)-dependent plasma membrane Ca2+ pump is present in these parasites.

L4 ANSWER 30 OF 41 MEDLINE on STN
ACCESSION NUMBER: 1990204182 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2108234
TITLE: Calcium-dependent protein phosphorylation in Babesia bovis and its role in growth regulation.
AUTHOR: Ray A; Quade J; Carson C A; Ray B K
CORPORATE SOURCE: Department of Veterinary Microbiology, University of Missouri, Columbia 65211.
SOURCE: The Journal of parasitology, (1990 Apr) Vol. 76, No. 2, pp. 153-61.
Journal code: 7803124. ISSN: 0022-3395.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 1 Jun 1990
Last Updated on STN: 1 Jun 1990
Entered Medline: 4 May 1990

AB Intracellular growth of protozoan parasite Babesia bovis has been followed to study the effect of some chemical agents on growth regulation. Using an in vitro parasite culture system we present evidence that the normal growth of the parasite is dependent upon available calcium and a Ca2(+)-binding protein, calmodulin, because sequestration of either of these 2 components from the culture medium causes inhibition of parasitic growth. Further studies demonstrate that the parasite contains a protein kinase that can phosphorylate a 40-kDa parasitic protein and its activity is regulated by calcium and calmodulin. Both the enzyme and its substrate are present in the membrane of the parasite. In addition, the parasite also contains a highly active protein kinase C activity that is documented by phosphorylating histone, a known substrate for protein kinase C. These findings suggest a possible correlation between the growth of parasite and calcium/calmodulin-dependent protein phosphorylation activity.

L4 ANSWER 31 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1990:94366 CAPLUS
DOCUMENT NUMBER: 112:94366
ORIGINAL REFERENCE NO.: 112:15955a,15958a
TITLE: Inhibition and activation of oat leaf calcium-dependent protein kinase by fatty acids
AUTHOR(S): Minichiello, J.; Polya, G. M.; Keane, P. J.
CORPORATE SOURCE: Dep. Biochem., La Trobe Univ., Bundoora, 3083, Australia
SOURCE: Plant Science (Shannon, Ireland) (1989), 65(2), 143-52
CODEN: PLSCE4; ISSN: 0168-9452
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Oat leaf Ca2+-dependent protein kinase (CDPK) was extensively purified from oat leaves by chromatog. on DEAE-cellulose, phenyl-Sepharose CL-4B, DEAE-Sephacel, Cibacron F3GA-Sepharose CL-6B, and Sephacryl S-200. The oat leaf CDPK (mol. weight, 79,000 from gel filtration) was nearly absolutely dependent upon micromolar free Ca2+ and millimolar Mg2+ for activity and phosphorylated a variety of substrates, including lysine-rich histone, casein, bovine serum albumin, avian myosin light chains, and a synthetic peptide corresponding to a phosphorylatable sequence of ribosomal protein S6. The oat leaf CDPK was inhibited by lanthanides, including Gd3+, Ho3+, Sm3+ and La3+, and was also inhibited by variety of inhibitors of calmodulin and of other plant CDPKs, including trifluoperazine, chlorpromazine, and calmidazolium. Behenic acid (IC50 20 μM) was a potent inhibitor of the enzyme. Other long chain fatty acids inhibited CDPK and the degree of inhibition decreased with decreasing chain length. Long-chain fatty acids (notably the fungal elicitor arachidonic acid) could also activate oat leaf CDPK in the absence of Ca2+.

L4 ANSWER 32 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 13
ACCESSION NUMBER: 1989:420769 CAPLUS
DOCUMENT NUMBER: 111:20769
ORIGINAL REFERENCE NO.: 111:3587a,3590a
TITLE: Stage-dependent inhibition of Plasmodium falciparum by potent calcium and calmodulin modulators
AUTHOR(S): Tanabe, Kazuyuki; Izumo, Akihisa; Kato, Mayumi; Miki, Atsushi; Doi, Syuichi
CORPORATE SOURCE: Med. Sch., Osaka City Univ., Osaka, 545, Japan
SOURCE: Journal of Protozoology (1989), 36(2), 139-43
CODEN: JPROAR; ISSN: 0022-3921
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of Ca2+ channel blockers, verapamil, nicardipine, and diltiazem, and of potent calmodulin (CaM) inhibitors, trifluoperazine (TFP), calmidazolium, W-7, and W-5, on P. falciparum in culture were examined Among Ca2+ blockers, nicardipine was the most potent with the 50% inhibitory concentration (IC50) of 4.3 μM at 72 h after culture. Parasites were more sensitive to calmidazolium and W-7, with IC50 of 3.4 and 4.5 μM, resp., than to TFP and W-5. All Ca2+ blockers and CaM inhibitors suppressed parasite development at later stages. Nicardipine, diltiazem, calmidazolium, and W-5 also retarded parasite development at earlier stages and/or subsequent growth following pretreatment. Verapamil, nicardipine, TFP, and calmidazolium reduced erythrocyte invasion by merozoites. Fluorescence microscopy with the cationic fluorescent dye rhodamine 123 revealed that nicardipine, TFP, and calmidazolium depolarized both the plasma membrane and mitochondrial membrane potentials of the parasite. It is therefore considered that although all Ca2+ and

CaM antagonists tested here influence parasite development at later stages, they are multifunctional, having effects not directly associated with Ca2+ channels or CaM.

L4 ANSWER 33 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 1989:20396 CAPLUS
DOCUMENT NUMBER: 110:20396
ORIGINAL REFERENCE NO.: 110:3417a,3420a
TITLE: The effect of K-252a, a potent microbial inhibitor of protein kinase, on activated cyclic nucleotide phosphodiesterase
AUTHOR(S): Matsuda, Yuzuru; Nakanishi, Satoshi; Nagasawa, Keiko; Iwahashi, Kazuyuki; Kase, Hiroshi
CORPORATE SOURCE: Tokyo Res. Lab., Kyowa Hakko Kogyo Co., Ltd., Machida, 194, Japan
SOURCE: Biochemical Journal (1988), 256(1), 75-80
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English
AB K-252a, an indole carbazol compound of microbial origin, inhibited activation of bovine brain phosphodiesterase induced by calmodulin (CaM), Na oleate, or limited proteolysis with almost equal potency. Kinetic anal. revealed that the CaM-activated phosphodiesterase (CaM-PDE) was competitively inhibited by K-252a with respect to CaM. On the other hand, inhibition of the trypsin-activated phosphodiesterase was competitive with respect to cAMP. Addition of a lower amount of phosphatidylserine or Na oleate to the reaction medium was efficacious in attenuating the inhibition of the CaM-PDE by W-7, compound 48/80, or calmidazolium but, in contrast, had no effect on the inhibition by K-252a. Furthermore, CaM-independent systems such as [3H]nitrendipine receptor binding or Na+ + K+-ATPase were influenced less by K-252a compared with W-7, compound 48/80, and calmidazolium. Thus, K-252a is an inhibitor of CaM-dependent cyclic nucleotide phosphodiesterase. Apparently, it inhibits the enzyme not only via CaM antagonism but possibly also by interfering with the enzyme.

L4 ANSWER 34 OF 41 MEDLINE on STN
ACCESSION NUMBER: 1989046862 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2847510
TITLE: The effect of calcium channel blockers and calmodulin inhibitors on the macrophage factor-stimulated synthesis of collagenase by rabbit chondrocytes.
AUTHOR: Nolan J C; Gathright C E; Wagner L E
CORPORATE SOURCE: Department of Pharmacology, A. H. Robins Company, Richmond, VA 23220.
SOURCE: Agents and actions, (1988 Aug) Vol. 25, No. 1-2, pp. 71-6.
Journal code: 0213341. ISSN: 0065-4299.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 8 Mar 1990
Entered Medline: 28 Nov 1988
AB Macrophages and monocytes secrete a factor(s) which can stimulate the synthesis of collagenase in synovial cells and in chondrocytes. Incubation of rabbit chondrocytes with macrophage conditioned medium (MCM) and with the calcium channel blockers, nifedipine, verapamil or diltiazem (up to 200 microM) had no effect on collagenase synthesis. However, TMB-8

(8-[N,N-diethylamino]-octyl 3,4,5-trimethoxybenzoate hydrochloride), an inhibitor of internal calcium movement, did inhibit the process with an IC50 of approximately 130 microM. The calmodulin antagonists, trifluoperazine, chlorpromazine and calmidazolium (R-24571) were effective inhibitors of the process with IC50's of 40 microM, 18 microM and 3.5 microM, respectively. Collagenase activity itself was not affected by these agents. The data suggests that calmodulin and/or internal calcium movement may play a role in the macrophage factor-stimulated synthesis of collagenase in rabbit chondrocytes.

L4 ANSWER 35 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1988:3314 CAPLUS
DOCUMENT NUMBER: 108:3314
ORIGINAL REFERENCE NO.: 108:643a,646a
TITLE: Calcium and calmodulin antagonists inhibit human malaria parasites (Plasmodium falciparum): implications for drug design
AUTHOR(S): Scheibel, L. W.; Colombani, P. M.; Hess, A. D.; Aikawa, M.; Atkinson, C. T.; Milhous, W. K.
CORPORATE SOURCE: Sch. Med., Unif. Serv. Univ. Health Sci., Bethesda, MD, 20814, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1987), 84(20), 7310-14
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Radioimmunoassay showed that free parasites contained CaM. Schizont-infected erythrocytes had CaM levels of 23.3 ng per 106 cells compared to normals (11.2 ng per 106 cells). CaM levels were proportional to parasite maturity. Immunoelectron microscopy identified CaM diffusely within the cytoplasm of mature parasites and at the apical end of merozoites within the ductule of rhoptries, which may explain the Ca2+ requirement for invasion. Cyclosporin A (CsA) was found by electron microscopic autoradiog. to concentrate in the food vacuole and to distribute within the cytoplasm of mature parasites. The binding of dansylated CsA to schizont-infected erythrocytes was higher than to normal erythrocytes, as analyzed by flow cytometry. Kinetic anal. revealed that binding was saturable for normal and infected erythrocytes and possibly free parasites. Competition for binding existed between dansylated ScA and native CsA, as well as for the CaM inhibitor W-7 and the classic antimalarial chloroquine. The in vitro growth of P. falciparum was sensitive to CaM antagonists, and in large part inhibition of the parasite was proportional to known anti-CaM potency. Antagonism existed between combinations of these drugs in multi-drug-resistant strains of P. falciparum, suggesting possible competition for the same binding site. In addition, the malaria parasite was also susceptible to Ca2+ antagonists.

L4 ANSWER 36 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1988:128674 CAPLUS
DOCUMENT NUMBER: 108:128674
ORIGINAL REFERENCE NO.: 108:21037a,21040a
TITLE: Calcium and calmodulin may not regulate the disease resistance and pisatin formation responses of Pisum sativum to chitosan or Fusarium solani
AUTHOR(S): Kendra, David F.; Hadwiger, Lee A.
CORPORATE SOURCE: Dep. Plant Pathol., Washington State Univ., Pullman, WA, 99164-6430, USA
SOURCE: Physiological and Molecular Plant Pathology (1987), 31(3), 337-48
CODEN: PMPPEZ; ISSN: 0885-5765

DOCUMENT TYPE: Journal
LANGUAGE: English
AB No correlation was found between the chitosan or F. solani-induced disease resistance responses in pea pod tissue and fluctuations in [Ca2+], inhibition of calmodulin, blockage of Ca2+ channels, or host membrane leakage. Addition of exogenous Ca2+ 3 h before or after chitosan or F. solani treatments of pea pod tissue failed to alter the host response within 6 h, the time when the host actively resists both the compatible (F. solani pisi) and incompatible (F. solani phaseoli) macroconidia. Addnl., Ca2+ applied exogenously 3 h before or after chitosan significantly altered the level of UV-absorbing material released from the host tissue; however, it failed to affect the chitosan's ability to elicit phytoalexin formation by 24 h. Addition of exogenous Ca2+ 3 h before or after inoculation with either the compatible or incompatible fungi did not significantly change the host response by 24 h. The addition of EGTA or Ca2+ channel antagonists with the chitosan treatments also failed to significantly alter the chitosan-induced host response, thereby suggesting that chitosan probably does not function in the pea system by causing a Ca2+ influx into the host tissue which might then activate the host's resistance response. Inhibition of calmodulin related activities by calmidazolium failed to inhibit the chitosan- or fungal -induced host response. These results suggest that the response(s) induced in pea pod tissue by chitosan treatment or fungal inoculation may not be mediated by Ca2+, calmodulin, or membrane leakage.

L4 ANSWER 37 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1988:128374 CAPLUS
DOCUMENT NUMBER: 108:128374
ORIGINAL REFERENCE NO.: 108:20985a,20988a
TITLE: Role of calmodulin in Plasmodium falciparum: implications for erythrocyte invasion by the merozoite
AUTHOR(S): Matsumoto, Yoshitsugu; Perry, George; Scheibel, L. William; Aikawa, Masamichi
CORPORATE SOURCE: Inst. Pathol., Case Western Reserve Univ., Cleveland, OH, USA
SOURCE: European Journal of Cell Biology (1987), 45(1), 36-43
CODEN: EJCBDN; ISSN: 0171-9335
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Calmodulin, a calcium-dependent modulator protein, was shown to be indispensable for in vitro growth of erythrocytic stages of the human malaria parasite, P. falciparum. When the potent calmodulin antagonists, W7, trifluoperazine (TFP) and R24571, were added to cultures of P. falciparum, they inhibited invasion of erythrocytes by merozoites, as well as maturation of schizonts. W5, a chlorine-deficient analog of W7, was a much weaker inhibitor than W7. The concns. of W5, W7, TFP and R24571 needed to produce 50% inhibition of schizont maturation were 63.5, 19, 18 and 8.5 μM, resp., while concns. needed to inhibit 50% the appearance of ring forms were only 19.5, 7, 8.4 and 4.5 μM, resp. All the antagonists were more effective at inhibiting the invasion of erythrocytes by merozoites than maturation of schizonts. Ca2+ depletion by EGTA also inhibited merozoite invasion of erythrocytes. Unlike W5, W7, TFP and R24571, cyclosporin A showed marked inhibition of schizont maturation at concns. that reduce ring form production Immunoelectron microscopy showed that calmodulin was concentrated at the apical end of both free and intraerythrocytic merozoites. No anticalmodulin immunoreactivity was observed in merozoites grown in the presence of 10 μM TFP, although the other calmodulin antagonists and EGTA did not significantly affect the calmodulin location in merozoites. These results suggest that the accumulation of calmodulin at the apical end of merozoites plays an important role during their attachment to and(or) invasion of the host

erythrocyte, possibly through activation of Ca2+ dependent processes.

L4 ANSWER 38 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1987:64616 CAPLUS
DOCUMENT NUMBER: 106:64616
ORIGINAL REFERENCE NO.: 106:10591a,10594a
TITLE: Calmodulin: biochemical, physiological, and morphological effects on Schistosoma mansoni
AUTHOR(S): Thompson, David P.; Chen, Guozhong; Sample, Allen K.; Semeyn, David R.; Bennett, James L.
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Michigan State Univ., East Lansing, MI, 48824, USA
SOURCE: American Journal of Physiology (1986), 251(6, Pt. 2), R1051-R1058
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Results of RIAs for the Ca2+-binding protein, calmodulin, revealed that this receptor constitutes 0.53% of the total protein in adult male S. mansoni. Schistosome calmodulin purified by Ca2+-dependent hydrophobic interaction chromatog. showed an apparent mol. weight of 19 kilodaltons, and its mobility on SDS-PAGE was influenced by the presence of Ca2+ but not the antischistosomal drug praziquantel. Calmodulin from the parasite effected a 4-fold stimulation of bovine heart cAMP phosphodiesterase; this process was inhibited by removal of Ca2+ with EGTA but not by praziquantel. Inhibition of calmodulin-activated processes with antipsychotic compds. in vitro resulted in a number of time- and concentration-dependent changes, including inhibition of schistosome calmodulin stimulation of bovine heart phosphodiesterase, disruption and depolarization of the parasite's tegument, and pos. inotropic effects on longitudinal musculature. Thus, calmodulin is a functional component of schistosomes and the role it serves is analogous to that obtained in other eukaryotes; i.e., it is an important component of numerous processes regulated, in part, by Ca2+.

L4 ANSWER 39 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 1987:2798 CAPLUS
DOCUMENT NUMBER: 106:2798
ORIGINAL REFERENCE NO.: 106:542h,543a
TITLE: Effect of calmodulin inhibitors on viability and mitochondrial potential of Plasmodium falciparum in culture
AUTHOR(S): Geary, T. G.; Divo, A. A.; Jensen, J. B.
CORPORATE SOURCE: Dep. Microbiol. Public Health, Michigan State Univ., East Lansing, MI, 48824-1101, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1986), 30(5), 785-8
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Calmodulin inhibitors are toxic for a variety of protozoa. Chlorpromazine, calmidazolium, and trifluoperazine inhibited the incorporation of [3H]hypoxanthine and [3H]phenylalanine into P. falciparum organisms in cultures with 50% inhibitory concns. varying from 5.1 μgM (with calmidazolium) to 48 μM (with chlorpromazine), the former being more sensitive than he latter. However, these concns. also immediately dissipated rhodamine 123 from the parasite mitochondria. Similar concns. inhibit other protozoa, as well as mammalian cells, and the possibility that mitochondrial function rather than that of calmodulin is the target of these drugs should be considered.

L4 ANSWER 40 OF 41 MEDLINE on STN

ACCESSION NUMBER: 1984272749 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6087356
TITLE: Infection of B lymphocytes by a human herpesvirus, Epstein-Barr virus, is blocked by calmodulin antagonists.
AUTHOR: Nemerow G R; Cooper N R
CONTRACT NUMBER: AI 17354 (United States NIAID NIH HHS)
CA 14692 (United States NCI NIH HHS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1984 Aug) Vol. 81, No. 15, pp. 4955-9.
Journal code: 7505876. ISSN: 0027-8424.
Report No.: NLM-PMC391611.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198409
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 19 Sep 1984

AB Epstein-Barr virus (EBV) is a human herpesvirus that selectively binds to and infects human B lymphocytes (B cells). In the studies presented here, we found that several phenothiazines, including trifluoperazine, chlorpromazine, prochlorpromazine, and promethazine, blocked EBV infectivity of isolated adult human B cells as measured either by outgrowth of transformed cell colonies or by [3H]thymidine incorporation. Trifluoperazine, chlorpromazine, and prochlorpromazine were equally effective with 20 microM fully inhibiting infectivity, whereas 100 microM promethazine was required for a comparable effect. Inhibition by trifluoperazine was partially reversible. Studies with radiolabeled EBV demonstrated that the inhibitors did not impair virus binding to B cells. Electron microscopic examination of B lymphocytes revealed that trifluoperazine reduced the number of large uncoated cell vacuoles and the number of membrane microvilli, indicating that this agent interfered with cell pinocytosis. This process was accompanied by inhibition of EBV endocytosis into B cells. Phenothiazines bind to and inhibit calmodulin, an intracellular calcium-binding protein that regulates several key enzymes, some of which directly affect cytoskeletal elements, although they also may interact nonspecifically with other cellular constituents. In this regard, haloperidol, a non-phenothiazine calmodulin antagonist, and R24571, a derivative of the antimycotic miconazole, which is a potent and highly specific calmodulin inhibitor, also blocked EBV infection. These studies suggest that calmodulin or a calmodulin-regulated cellular enzyme(s) is involved in normal cellular endocytic processes in B lymphocytes and thereby in the early stages of EBV infection.

L4 ANSWER 41 OF 41 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1975:593323 CAPLUS
DOCUMENT NUMBER: 83:193323
ORIGINAL REFERENCE NO.: 83:30413a,30416a
TITLE: Imidazolium salts
INVENTOR(S): Janssen, Paul A. J.; Heeres, Jan; Hermans, Hubert K. F.
PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., USA
SOURCE: Ger. Offen., 100 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
DE 2504114	A1	19750807	DE 1975-2504114		19750131	<--
DE 2504114	C2	19890316				
US 3991202	A	19761109	US 1974-525142		19741119	<--
GB 1489112	A	19771019	GB 1975-2829		19750122	<--
NL 7501066	A	19750804	NL 1975-1066		19750129	<--
NL 186767	B	19900917				
NL 186767	C	19910218				
JP 50106959	A	19750822	JP 1975-11455		19750129	<--
JP 60009030	B	19850307				
CA 1049535	A1	19790227	CA 1975-218962		19750129	<--
FR 2329657	A1	19770527	FR 1975-2944		19750130	<--
BE 825028	A2	19750731	BE 1975-152916		19750131	<--
PRIORITY APPLN. INFO.:			US 1974-438310	A	19740131	
			US 1974-525142	A	19741119	

GI For diagram(s), see printed CA Issue.

AB Fungicidal and bactericidal imidazolium salts (.apprx.160 compds.) were prepared by quaternization. Thus I was obtained by treating the 1-substituted imidazole with ClCH2CONHC6H4Cl-2. I had a min. inhibitory concentration against Trichophyton rubrum of 1 γ/ml and against Microsporum canis of 10 γ/ml.

=> s l4 and (adenylyl cyclase or adenyl cyclase or adenylate cyclase)
L5 1 L4 AND (ADENYLYL CYCLASE OR ADENYL CYCLASE OR ADENYLATE CYCLASE)

=> d l5 ibib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:218830 CAPLUS
DOCUMENT NUMBER: 139:111113
TITLE: Small ligands modulating the activity of mammalian adenylyl cyclases: A novel mode of inhibition by calmidazolium
AUTHOR(S): Haunso, Anders; Simpson, James; Antoni, Ferenc A.
CORPORATE SOURCE: Department of Neuroscience, University of Edinburgh, Edinburgh, UK
SOURCE: Molecular Pharmacology (2003), 63(3), 624-631
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mol. cloning of membrane-spanning mammalian adenylyl cyclases (ACs) has led to the discovery of nine different isotypes, making ACs potentially useful therapeutic targets. This study investigated the mechanism by which fungicidal nitroimidazole compds. modulate AC activity. Current evidence indicates that biol. control of AC activity occurs through the cytosolic domains. Hence, full-length ACII, ACIX, and recombinant fusion proteins composed of the cytoplasmic loops of human ACIX or the first and second cytoplasmic loops of rat ACV and ACII, resp., were expressed in human embryonic kidney 293 cells. The AC activities of the resp. proteins were characterized, and their modulation by nitroimidazoles was investigated. Calmidazolium inhibited the activities of both full-length ACs and soluble fusion proteins (IC50, .apprx.10 μM). Inhibition of ACIX by calmidazolium was mediated by direct interaction with the catalytic core in a noncompetitive fashion. ACIX was essentially

insensitive to 2'-deoxyadenosine 3'-monophosphate, a known blocker of AC activity. The ACV-ACII fusion protein was inhibited by calmidazolium (IC50, .apprx.20 μM) as well as by 2'-deoxyadenosine 3'-AMP (IC50, .apprx.2 μM), in a manner indicating independent mechanisms of action. Taken together, the data demonstrate that ACIX is insensitive to adenosine analogs and that calmidazolium inhibits AC activity by a novel, noncompetitive mechanism.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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NEWS 4	NOV 26	CHEMSAFE now available on STN Easy
NEWS 5	NOV 26	Two new SET commands increase convenience of STN searching
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NEWS 13	FEB 06	Patent sequence location (PSL) data added to USGENE
NEWS 14	FEB 10	COMPENDEX reloaded and enhanced
NEWS 15	FEB 11	WTEXTILES reloaded and enhanced
NEWS 16	FEB 19	New patent-examiner citations in 300,000 CA/CAplus patent records provide insights into related prior art
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=> s soluble adenylyl cyclase
L1         167 SOLUBLE ADENYLYL CYCLASE

=> s l1 and (parasit? or antiparasit? or fung? or antifung? or microb? or
antimicrob?)
L2          11 L1 AND (PARASIT? OR ANTIPARASIT? OR FUNG? OR ANTIFUNG? OR MICROB
               ? OR ANTIMICROB?)

=> d l2 ibib abs 1-11

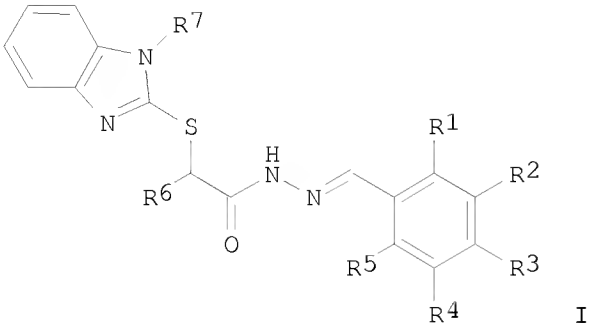
L2   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2005:714054  CAPLUS
DOCUMENT NUMBER:         143:171291
TITLE:                   Calcium-sensing soluble adenylyl
                         cyclase mediates TNF signal transduction in
                         human neutrophils
AUTHOR(S):               Han, Hyunsil; Stessin, Alexander; Roberts, Julia;
                         Hess, Kenneth; Gautam, Narinder; Kamenetsky,
                         Margarita; Lou, Olivia; Hyde, Edward; Nathan, Noah;
                         Muller, William A.; Buck, Jochen; Levin, Lonny R.;
                         Nathan, Carl
CORPORATE SOURCE:        Department of Microbiology and Immunology, The
                         Rockefeller University, New York, NY, 10021, USA
SOURCE:                  Journal of Experimental Medicine (2005), 202(3),
                         353-361
                         CODEN: JEMEAV; ISSN: 0022-1007
```

PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Through chemical screening, we identified a pyrazolone that reversibly blocked the activation of phagocyte oxidase (phox) in human neutrophils in response to tumor necrosis factor (TNF) or formylated peptide. The pyrazolone spared activation of phox by phorbol ester or bacteria, bacterial killing, TNF-induced granule exocytosis and phox assembly, and endothelial transmigration. We traced the pyrazolone's mechanism of action to inhibition of TNF-induced intracellular Ca2+ elevations, and identified a nontransmembrane ("soluble") adenylyl cyclase (sAC) in neutrophils as a Ca2+-sensing source of cAMP. A sAC inhibitor mimicked the pyrazolone's effect on phox. Both compds. blocked TNF-induced activation of Rap1A, a phox-associated guanosine triphosphatase that is regulated by cAMP. Thus, TNF turns on phox through a Ca2+-triggered, sAC-dependent process that may involve activation of Rap1A. This pathway may offer opportunities to suppress oxidative damage during inflammation without blocking antimicrobial function.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:696742 CAPLUS
DOCUMENT NUMBER: 143:166722
TITLE: Soluble adenylyl cyclase inhibitors for therapeutic use
INVENTOR(S): Buck, Jochen; Levin, Lonny R.; Muhlschlegel, Fritz A.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA; University of Kent
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005070419	A1	20050804	WO 2005-US1807		20050120
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2553848	A1	20050804	CA 2005-2553848		20050120
EP 1706114	A1	20061004	EP 2005-711707		20050120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS					
IN 2006KN02381	A	20070525	IN 2006-KN2381		20060821
US 20070244174	A1	20071018	US 2007-586929		20070524
PRIORITY APPLN. INFO.:			US 2004-537864P	P	20040121
			WO 2005-US1807	W	20050120

OTHER SOURCE(S): MARPAT 143:166722
GI



I

AB The invention discloses a method for treating a disorder mediated by soluble adenylyl cyclase in a subject. The method involves administering to a subject an effective amount of a compound disclosed herein that modulates soluble adenylyl cyclase, under conditions effective to treat the disorder mediated by soluble adenylyl cyclase. The invention also discloses a method for treating a disorder mediated by soluble adenylyl cyclase in a subject, where the disorder is selected from the group consisting of learning or memory disorders, malaria, fungal infection, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, and peripheral neuropathy. The method involves modulating soluble adenylyl cyclase in the subject. Another aspect of the invention relates to a method of modulating soluble adenylyl cyclase. The method involves contacting eukaryotic cells with a compound that modulates soluble adenylyl cyclase, under conditions effective to modulate soluble adenylyl cyclase. Compds. of the invention include I [R1 = H, OH, alkyloxy, halo; R2, R5 = H, halo; R3 = H, OH; R4 = H, alkyloxy, halo; R6 = H, alkyl; R7 = H, CH2R8; R8 = H, alkyl, (un)substituted Ph; with proviso that at least one of R1-R4 is halo].

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2005:243790 CAPLUS

DOCUMENT NUMBER: 143:362006

TITLE: Guanylyl cyclases across the tree of life

AUTHOR(S): Schaap, Pauline

CORPORATE SOURCE: School of Life Sciences, University of Dundee, UK

SOURCE: Frontiers in Bioscience (2005), 10(2), 1485-1498
CODEN: FRBIF6; ISSN: 1093-4715
URL: http://www.bioscience.org/asp/getfile.asp?FileName=/2005/v10/af/1633/1633.pdf

PUBLISHER: Frontiers in Bioscience

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

AB A review. Here, the author explores the origins, diversity, and functions of guanylyl cyclases (GCs) in cellular organisms. In eukaryotes, both cGMP and cAMP are produced by the conserved class III cyclase domains, whereas prokaryotes use 5 more unrelated catalysts for cyclic nucleotide synthesis. The class III domain is found embedded in proteins with a large variety of membrane topologies and other functional domains, but the vertebrate GCs take only 2 forms: the receptor GCs with a single transmembrane domain and the soluble GCs (sGCs) with a heme binding domain. The invertebrates addnl. show a sGC that cannot bind heme, whereas the more basal metazoans may lack the heme binding enzymes altogether.

Fungi, the closest relatives of the metazoans, completely lack GCs, but they appear again in the Dictyostelids, the next relative in line. Remarkably, the 2 Dictyostelid GCs have little in common with the vertebrate enzymes. There is a sGC, which shows greatest sequence and structural similarity to the vertebrate soluble adenylyl cyclase (sAC), and a membrane-bound form with the same configuration as the dodecahelical ACs of vertebrates. There is a difference, in that the pseudosym. C1 and C2 catalytic domains have swapped position in the Dictyostelium enzyme. Unlike the vertebrate GCs, the Dictyostelium enzymes are activated by heterotrimeric G-proteins. Swapped C1 and C2 domains are also found in the structurally similar GCs of ciliates and apicomplexans, but these enzymes addnl. harbor an N-terminal ATPase module with ten transmembrane domains. G-protein regulation could not be demonstrated for these enzymes. Higher plants lack class III cyclase domains, but an unexplored wealth of GCs is present in the green alga Chlamydomonas. Progenitors of all structural variants of the eukaryotic GCs are found among the prokaryotic ACs. This and the close similarity of many GCs to ACs suggests a paraphyletic origin for the eukaryotic enzymes with multiple events of conversion of substrate specificity.

REFERENCE COUNT: 151 THERE ARE 151 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:828625 CAPLUS

DOCUMENT NUMBER: 142:405087

TITLE: Conservation of functional domain structure in bicarbonate-regulated "soluble" adenylyl cyclases in bacteria and eukaryotes

AUTHOR(S): Kobayashi, Mime; Buck, Jochen; Levin, Lonny R.

CORPORATE SOURCE: Department of Pharmacology, Weill Medical College of Cornell University, New York, NY, 10021, USA

SOURCE: Dev. Genes Evol. (2004), 214(10), 503-509
CODEN: DGEVFT; ISSN: 0949-944X

PUBLISHER: Springer GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Soluble adenylyl cyclase (sAC) is an evolutionarily conserved bicarbonate sensor. In mammals, it is responsible for bicarbonate-induced, cAMP-dependent processes in sperm required for fertilization and postulated to be involved in other bicarbonate- and carbon dioxide-dependent functions throughout the body. Among eukaryotes, sAC-like cyclases have been detected in mammals and in the fungi Dictyostelium; these enzymes display extensive similarity extending through two cyclase catalytic domains and a long carboxy terminal extension. sAC-like cyclases are also found in a number of bacterial phyla (Cyanobacteria, Actinobacteria, and Proteobacteria), but these enzymes generally possess only a single catalytic domain and little, if any, homol. with the remainder of the mammalian protein. Database mining through a number of recently sequenced genomes identified sAC orthologues in addnl. metazoan phyla (Arthropoda and Chordata) and addnl. bacterial phyla (Chloroflexi). Interestingly, the Chloroflexi sAC-like cyclases, a family of three enzymes from the thermophilic eubacterium, Chloroflexus aurantiacus, are more similar to eukaryotic sAC-like cyclases (i.e., mammalian sAC and Dictyostelium SgcA) than they are to other bacterial adenylyl cyclases (ACs) (i.e., from Cyanobacteria). The Chloroflexus sAC-like cyclases each possess two cyclase catalytic domains and extensive similarity with mammalian enzymes through their carboxy termini. We cloned one of the Chloroflexus sAC-like cyclases and confirmed it to be stimulated by bicarbonate. These data extend the

family of organisms possessing bicarbonate-responsive ACs to numerous phyla within the bacterial and eukaryotic kingdoms.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:969221 CAPLUS
DOCUMENT NUMBER: 138:301038
TITLE: Deducing the origin of soluble adenylyl cyclase, a gene lost in multiple lineages
AUTHOR(S): Roelofs, Jeroen; Van Haastert, Peter J. M.
CORPORATE SOURCE: GBB, Department of Biochemistry, University of Groningen, Groningen, 9747 AG, Neth.
SOURCE: Molecular Biology and Evolution (2002), 19(12), 2239-2246
CODEN: MBEVEO; ISSN: 0737-4038
PUBLISHER: Society for Molecular Biology and Evolution
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The family of eukaryotic adenylyl cyclases consists of a very large group of 12 transmembrane adenylyl cyclases and a very small group of soluble adenylyl cyclase (sAC). Orthologs of human sAC are present in rat, Dictyostelium, and bacteria but absent from the completely sequenced genomes of Drosophila melanogaster, Caenorhabditis elegans, Arabidopsis thaliana, and Saccharomyces cerevisiae. SAC consists of two cyclase domains and a long .apprx.1000 amino acid C-terminal (sCKH) region. This sCKH region and one cyclase domain have been found in only four bacterial genes; the sCKH region was also detected in bacterial Lux-transcription factors and in complex bacterial and fungal kinases. The phylogenies of the kinase and cyclase domains are identical to the phylogeny of the corresponding sCKH domain, suggesting that the sCKH region fused with the other domains early during evolution in bacteria. The amino acid sequences of sAC proteins yield divergence times from the human lineage for rat and Dictyostelium that are close to the reported divergence times of many other proteins in these species. The combined results suggest that the sCKH region was fused with one cyclase domain in bacteria, and a second cyclase domain was added in bacteria or early eukaryotes. The sAC was retained in a few bacteria and throughout the entire evolution of the human lineage but lost independently from many bacteria and from the lineages of plants, yeast, worms, and flies. We conclude that within the family of adenylyl cyclases, soluble AC was poorly fixed during evolution, whereas membrane-bound AC has expanded to form the subgroups of prevailing adenylyl and guanylyl cyclases.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:239715 CAPLUS
DOCUMENT NUMBER: 136:365612
TITLE: Characterization of two unusual guanylyl cyclases from Dictyostelium
AUTHOR(S): Roelofs, Jeroen; Van Haastert, Peter J. M.
CORPORATE SOURCE: Department of Biochemistry, University of Groningen, Groningen, 9747 AG, Neth.
SOURCE: Journal of Biological Chemistry (2002), 277(11), 9167-9174
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Guanylyl cyclase A (GCA) and soluble guanylyl cyclase (sGC) encode GCs in Dictyostelium and have a topol. similar to 12-transmembrane and soluble adenylyl cyclase, resp. We demonstrate that all detectable GC activity is lost in a cell line in which both genes have been inactivated. Cell lines with one gene inactivated were used to characterize the other guanylyl cyclase (i.e. GCA in sgc- null cells and sGC in gca- null cells). Despite the different topologies, the enzymes have many properties in common. In vivo, extracellular cAMP activates both enzymes via a G-protein-coupled receptor. In vitro, both enzymes are activated by GTPγS (Ka = 11 and 8 μM for GCA and sGC, resp.). The addition of GTPγS leads to a 1.5-fold increase of Vmax and a 3.5-fold increase of the affinity for GTP. Ca2+ inhibits both GCA and sGC with Ki of about 50 and 200 nM, resp. Other biochem. properties are very different; GCA is expressed mainly during growth and multicellular development, whereas sGC is expressed mainly during cell aggregation. Folic acid and cAMP activate GCA maximally about 2.5-fold, whereas sGC is activated about 8-fold. Osmotic stress strongly stimulates sGC but has no effect on GCA activity. Finally, GCA is exclusively membrane-bound and is active mainly with Mg2+, whereas sGC is predominantly soluble and more active with Mn2+.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:643259 CAPLUS

DOCUMENT NUMBER: 135:328630

TITLE: The Dictyostelium homologue of mammalian soluble adenylyl cyclase encodes a guanylyl cyclase

AUTHOR(S): Roelofs, Jeroen; Meima, Marcel; Schaap, Pauline; Van Haastert, Peter J. M.

CORPORATE SOURCE: GBB, Department of Biochemistry, University of Groningen, Groningen, 9747 AG, Neth.

SOURCE: EMBO Journal (2001), 20(16), 4341-4348
CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new Dictyostelium discoideum cyclase gene was identified that encodes a protein (sGC) with 35% similarity to mammalian soluble adenylyl cyclase (sAC). Gene disruption of sGC has no effect on adenylyl cyclase activity and results in a >10-fold reduction in guanylyl cyclase activity. The scg-null mutants show reduced chemotactic sensitivity and aggregate poorly under stringent conditions. With Mn2+/GTP as substrate, most of the sGC activity is soluble, but with the more physiol. Mg2+/GTP the activity is detected in membranes and stimulated by GTPγS. Unexpectedly, orthologs of sGC and sAC are present in bacteria and vertebrates, but absent from Drosophila melanogaster, Caenorhabditis elegans, Arabidopsis thaliana and Saccharomyces cerevisiae.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 11 MEDLINE on STN

ACCESSION NUMBER: 2005401188 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16043520

TITLE: Calcium-sensing soluble adenylyl cyclase mediates TNF signal transduction in human neutrophils.

AUTHOR: Han Hyunsil; Stessin Alexander; Roberts Julia; Hess Kenneth; Gautam Narinder; Kamenetsky Margarita; Lou Olivia; Hyde Edward; Nathan Noah; Muller William A; Buck Jochen;

Levin Lonny R; Nathan Carl
CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021, USA.
CONTRACT NUMBER: AI46382 (United States NIAID NIH HHS)
GM62328 (United States NIGMS NIH HHS)
HD38722 (United States NICHD NIH HHS)
HD42060 (United States NICHD NIH HHS)
HL46849 (United States NHLBI NIH HHS)
HL64774 (United States NHLBI NIH HHS)
SOURCE: The Journal of experimental medicine, (2005 Aug 1) Vol. 202, No. 3, pp. 353-61. Electronic Publication: 2005-07-25.
Journal code: 2985109R. ISSN: 0022-1007.
Report No.: NLM-PMC2213086.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 3 Aug 2005
Last Updated on STN: 30 Sep 2005
Entered Medline: 29 Sep 2005

AB Through chemical screening, we identified a pyrazolone that reversibly blocked the activation of phagocyte oxidase (phox) in human neutrophils in response to tumor necrosis factor (TNF) or formylated peptide. The pyrazolone spared activation of phox by phorbol ester or bacteria, bacterial killing, TNF-induced granule exocytosis and phox assembly, and endothelial transmigration. We traced the pyrazolone's mechanism of action to inhibition of TNF-induced intracellular Ca2+ elevations, and identified a nontransmembrane ("soluble") adenylyl cyclase (sAC) in neutrophils as a Ca2+-sensing source of cAMP. A sAC inhibitor mimicked the pyrazolone's effect on phox. Both compounds blocked TNF-induced activation of Rap1A, a phox-associated guanosine triphosphatase that is regulated by cAMP. Thus, TNF turns on phox through a Ca2+-triggered, sAC-dependent process that may involve activation of Rap1A. This pathway may offer opportunities to suppress oxidative damage during inflammation without blocking antimicrobial function.

L2 ANSWER 9 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2005144524 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15769639
TITLE: Guanylyl cyclases across the tree of life.
AUTHOR: Schaap Pauline
CORPORATE SOURCE: School of Life Sciences, University of Dundee, UK. p.schaap@dundee.ac.uk. <p.schaap@dundee.ac.uk>
SOURCE: Frontiers in bioscience : a journal and virtual library, (2005) Vol. 10, pp. 1485-98. Electronic Publication: 2005-05-01. Ref: 151
Journal code: 9709506. E-ISSN: 1093-4715.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200609
ENTRY DATE: Entered STN: 22 Mar 2005
Last Updated on STN: 14 Dec 2005
Entered Medline: 18 Sep 2006

AB This review explores the origins, diversity and functions of guanylyl cyclases in cellular organisms. In eukaryotes both cGMP and cAMP are produced by the conserved class III cyclase domains, while prokaryotes use five more unrelated catalysts for cyclic nucleotide synthesis. The class III domain is found embedded in proteins with a large variety of membrane topologies and other functional domains, but the vertebrate guanylyl cyclases take only two forms, the receptor guanylyl cyclases with single transmembrane domain and the soluble enzymes with heme binding domain. The invertebrates additionally show a soluble guanylyl cyclase that cannot bind heme, while the more basal metazoans may lack the heme binding enzymes altogether. Fungi, the closest relatives of the metazoans, completely lack guanylyl cylases, but they appear again in the Dictyostelids, the next relative in line. Remarkably, the two Dictyostelid guanylyl cyclases have little in common with the vertebrate enzymes. There is a soluble guanylyl cyclase, which shows greatest sequence and structural similarity to the vertebrate soluble adenylyl cyclase, and a membrane-bound form with the same configuration as the dodecahelical adenylyl cyclases of vertebrates. There is a difference, the pseudosymmetric C1 and C2 catalytic domains have swapped position in the Dictyostelium enzyme. Unlike the vertebrate guanylyl cyclases, the Dictyostelium enzymes are activated by heterotrimeric G-proteins. Swapped C1 and C2 domains are also found in the structurally similar guanylyl cyclases of ciliates and apicomplexans, but these enzymes additionally harbour an amino-terminal ATPase module with ten transmembrane domains. G-protein regulation could not be demonstrated for these enzymes. Higher plants lack class III cyclase domains, but an unexplored wealth of guanylyl cyclases is present in the green alga Chlamydomonas. Progenitors of all structural variants of the eukaryote guanylyl cyclases are found among the prokaryote adenylyl cyclases. This and the close similarity of many guanylyl cyclases to adenylyl cyclases suggests a paraphyletic origin for the eukaryote enzymes with multiple events of conversion of substrate specificity.

L2 ANSWER 10 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2004509993 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15322879
TITLE: Conservation of functional domain structure in bicarbonate-regulated "soluble" adenylyl cyclases in bacteria and eukaryotes.
AUTHOR: Kobayashi Mime; Buck Jochen; Levin Lonny R
CORPORATE SOURCE: Department of Pharmacology, Weill Medical College of Cornell University, 1300 York Avenue, Room E-505, New York, NY 10021, USA.. mime@nttbrl.jp
CONTRACT NUMBER: GM62328 (United States NIGMS NIH HHS)
HD38722 (United States NICHD NIH HHS)
HD42060 (United States NICHD NIH HHS)
SOURCE: Development genes and evolution, (2004 Oct) Vol. 214, No. 10, pp. 503-9. Electronic Publication: 2004-08-20.
Journal code: 9613264. ISSN: 0949-944X.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 14 Oct 2004
Last Updated on STN: 18 Mar 2005
Entered Medline: 17 Mar 2005

AB Soluble adenylyl cyclase (sAC) is an evolutionarily conserved bicarbonate sensor. In mammals, it is

responsible for bicarbonate-induced, cAMP-dependent processes in sperm required for fertilization and postulated to be involved in other bicarbonate- and carbon dioxide-dependent functions throughout the body. Among eukaryotes, sAC-like cyclases have been detected in mammals and in the fungi Dictyostelium; these enzymes display extensive similarity extending through two cyclase catalytic domains and a long carboxy terminal extension. sAC-like cyclases are also found in a number of bacterial phyla (Cyanobacteria, Actinobacteria, and Proteobacteria), but these enzymes generally possess only a single catalytic domain and little, if any, homology with the remainder of the mammalian protein. Database mining through a number of recently sequenced genomes identified sAC orthologues in additional metazoan phyla (Arthropoda and Chordata) and additional bacterial phyla (Chloroflexi). Interestingly, the Chloroflexi sAC-like cyclases, a family of three enzymes from the thermophilic eubacterium, Chloroflexus aurantiacus, are more similar to eukaryotic sAC-like cyclases (i.e., mammalian sAC and Dictyostelium SgcA) than they are to other bacterial adenylyl cyclases (ACs) (i.e., from Cyanobacteria). The Chloroflexus sAC-like cyclases each possess two cyclase catalytic domains and extensive similarity with mammalian enzymes through their carboxy termini. We cloned one of the Chloroflexus sAC-like cyclases and confirmed it to be stimulated by bicarbonate. These data extend the family of organisms possessing bicarbonate-responsive ACs to numerous phyla within the bacterial and eukaryotic kingdoms.

L2 ANSWER 11 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2002688843 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12446814
TITLE: Deducing the origin of soluble adenylyl cyclase, a gene lost in multiple lineages.
AUTHOR: Roelofs Jeroen; Van Haastert Peter J M
CORPORATE SOURCE: GBB, Department of Biochemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.
SOURCE: Molecular biology and evolution, (2002 Dec) Vol. 19, No. 12, pp. 2239-46.
Journal code: 8501455. ISSN: 0737-4038.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 14 Dec 2002
Last Updated on STN: 29 May 2003
Entered Medline: 28 May 2003

AB The family of eukaryotic adenylyl cyclases consists of a very large group of 12 transmembrane adenylyl cyclases and a very small group of soluble adenylyl cyclase (sAC). Orthologs of human sAC are present in rat Dictyostelium and bacteria but absent from the completely sequenced genomes of Drosophila melanogaster, Caenorhabditis elegans, Arabidopsis thaliana, and Saccharomyces cereviciae. sAC consists of two cyclase domains and a long approximately 1,000 amino acid C-terminal (sCKH) region. This sCKH region and one cyclase domain have been found in only four bacterial genes; the sCKH region was also detected in bacterial Lux-transcription factors and in complex bacterial and fungal kinases. The phylogenies of the kinase and cyclase domains are identical to the phylogeny of the corresponding sCKH domain, suggesting that the sCKH region fused with the other domains early during evolution in bacteria. The amino acid sequences of sAC proteins yield divergence times from the human lineage for rat and Dictyostelium that are close to the reported divergence times of many other proteins in these species. The combined results suggest that the sCKH region was fused with one cyclase domain in bacteria, and a

second cyclase domain was added in bacteria or early eukaryotes. The sAC was retained in a few bacteria and throughout the entire evolution of the human lineage but lost independently from many bacteria and from the lineages of plants, yeast, worms, and flies. We conclude that within the family of adenylyl cyclases, soluble AC was poorly fixed during evolution, whereas membrane-bound AC has expanded to form the subgroups of prevailing adenylyl and guanylyl cyclases.

=> s l2 and inhibit?
L3 4 L2 AND INHIBIT?

=> d l3 ibib abs 1-4

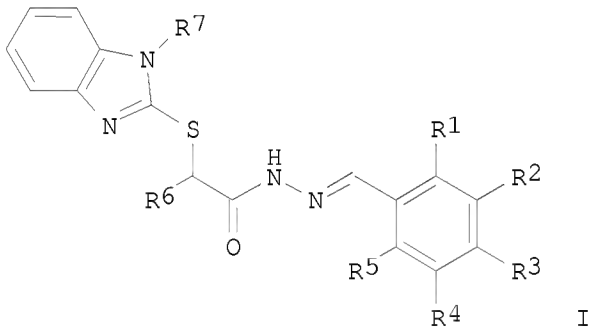
L3 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:714054 CAPLUS
DOCUMENT NUMBER: 143:171291
TITLE: Calcium-sensing soluble adenylyl cyclase mediates TNF signal transduction in human neutrophils
AUTHOR(S): Han, Hyunsil; Stessin, Alexander; Roberts, Julia; Hess, Kenneth; Gautam, Narinder; Kamenetsky, Margarita; Lou, Olivia; Hyde, Edward; Nathan, Noah; Muller, William A.; Buck, Jochen; Levin, Lonny R.; Nathan, Carl
CORPORATE SOURCE: Department of Microbiology and Immunology, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of Experimental Medicine (2005), 202(3), 353-361
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Through chemical screening, we identified a pyrazolone that reversibly blocked the activation of phagocyte oxidase (phox) in human neutrophils in response to tumor necrosis factor (TNF) or formylated peptide. The pyrazolone spared activation of phox by phorbol ester or bacteria, bacterial killing, TNF-induced granule exocytosis and phox assembly, and endothelial transmigration. We traced the pyrazolone's mechanism of action to inhibition of TNF-induced intracellular Ca2+ elevations, and identified a nontransmembrane ("soluble") adenylyl cyclase (sAC) in neutrophils as a Ca2+-sensing source of cAMP. A sAC inhibitor mimicked the pyrazolone's effect on phox. Both compds. blocked TNF-induced activation of Rap1A, a phox-associated guanosine triphosphatase that is regulated by cAMP. Thus, TNF turns on phox through a Ca2+-triggered, sAC-dependent process that may involve activation of Rap1A. This pathway may offer opportunities to suppress oxidative damage during inflammation without blocking antimicrobial function.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:696742 CAPLUS
DOCUMENT NUMBER: 143:166722
TITLE: Soluble adenylyl cyclase inhibitors for therapeutic use
INVENTOR(S): Buck, Jochen; Levin, Lonny R.; Muhlschlegel, Fritz A.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA; University of Kent
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005070419	A1	20050804	WO 2005-US1807	20050120
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2553848	A1	20050804	CA 2005-2553848	20050120
EP 1706114	A1	20061004	EP 2005-711707	20050120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
IN 2006KN02381	A	20070525	IN 2006-KN2381	20060821
US 20070244174	A1	20071018	US 2007-586929	20070524
PRIORITY APPLN. INFO.:			US 2004-537864P P	20040121
			WO 2005-US1807 W	20050120

OTHER SOURCE(S): MARPAT 143:166722
GI



I

AB The invention discloses a method for treating a disorder mediated by soluble adenylyl cyclase in a subject. The method involves administering to a subject an effective amount of a compound disclosed herein that modulates soluble adenylyl cyclase, under conditions effective to treat the disorder mediated by soluble adenylyl cyclase. The invention also discloses a method for treating a disorder mediated by soluble adenylyl cyclase in a subject, where the disorder is selected from the group consisting of learning or memory disorders, malaria, fungal infection, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, and peripheral neuropathy. The method involves modulating soluble adenylyl cyclase in the subject. Another aspect of the invention relates to a method of modulating soluble adenylyl cyclase. The method involves contacting eukaryotic cells with a compound that modulates soluble adenylyl cyclase,

under conditions effective to modulate soluble adenylyl cyclase. Compds. of the invention include I [R1 = H, OH, alkyloxy, halo; R2, R5 = H, halo; R3 = H, OH; R4 = H, alkyloxy, halo; R6 = H, alkyl; R7 = H, CH2R8; R8 = H, alkyl, (un)substituted Ph; with proviso that at least one of R1–R4 is halo].

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:239715 CAPLUS

DOCUMENT NUMBER: 136:365612

TITLE: Characterization of two unusual guanylyl cyclases from Dictyostelium

AUTHOR(S): Roelofs, Jeroen; Van Haastert, Peter J. M.

CORPORATE SOURCE: Department of Biochemistry, University of Groningen, Groningen, 9747 AG, Neth.

SOURCE: Journal of Biological Chemistry (2002), 277(11), 9167-9174
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Guanylyl cyclase A (GCA) and soluble guanylyl cyclase (sGC) encode GCs in Dictyostelium and have a topol. similar to 12-transmembrane and soluble adenylyl cyclase, resp. We demonstrate that all detectable GC activity is lost in a cell line in which both genes have been inactivated. Cell lines with one gene inactivated were used to characterize the other guanylyl cyclase (i.e. GCA in sgc- null cells and sGC in gca- null cells). Despite the different topologies, the enzymes have many properties in common. In vivo, extracellular cAMP activates both enzymes via a G-protein-coupled receptor. In vitro, both enzymes are activated by GTPγS (Ka = 11 and 8 μM for GCA and sGC, resp.). The addition of GTPγS leads to a 1.5-fold increase of Vmax and a 3.5-fold increase of the affinity for GTP. Ca2+ inhibits both GCA and sGC with Ki of about 50 and 200 nM, resp. Other biochem. properties are very different; GCA is expressed mainly during growth and multicellular development, whereas sGC is expressed mainly during cell aggregation. Folic acid and cAMP activate GCA maximally about 2.5-fold, whereas sGC is activated about 8-fold. Osmotic stress strongly stimulates sGC but has no effect on GCA activity. Finally, GCA is exclusively membrane-bound and is active mainly with Mg2+, whereas sGC is predominantly soluble and more active with Mn2+.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 4 MEDLINE on STN

ACCESSION NUMBER: 2005401188 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16043520

TITLE: Calcium-sensing soluble adenylyl cyclase mediates TNF signal transduction in human neutrophils.

AUTHOR: Han Hyunsil; Stessin Alexander; Roberts Julia; Hess Kenneth; Gautam Narinder; Kamenetsky Margarita; Lou Olivia; Hyde Edward; Nathan Noah; Muller William A; Buck Jochen; Levin Lonny R; Nathan Carl

CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021, USA.

CONTRACT NUMBER: AI46382 (United States NIAID NIH HHS)
GM62328 (United States NIGMS NIH HHS)
HD38722 (United States NICHD NIH HHS)
HD42060 (United States NICHD NIH HHS)

HL46849 (United States NHLBI NIH HHS)
HL64774 (United States NHLBI NIH HHS)
SOURCE: The Journal of experimental medicine, (2005 Aug 1) Vol. 202, No. 3, pp. 353-61. Electronic Publication: 2005-07-25.
Journal code: 2985109R. ISSN: 0022-1007.
Report No.: NLM-PMC2213086.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 3 Aug 2005
Last Updated on STN: 30 Sep 2005
Entered Medline: 29 Sep 2005

AB Through chemical screening, we identified a pyrazolone that reversibly blocked the activation of phagocyte oxidase (phox) in human neutrophils in response to tumor necrosis factor (TNF) or formylated peptide. The pyrazolone spared activation of phox by phorbol ester or bacteria, bacterial killing, TNF-induced granule exocytosis and phox assembly, and endothelial transmigration. We traced the pyrazolone's mechanism of action to inhibition of TNF-induced intracellular Ca2+ elevations, and identified a nontransmembrane ("soluble") adenylyl cyclase (sAC) in neutrophils as a Ca2+-sensing source of cAMP. A sAC inhibitor mimicked the pyrazolone's effect on phox. Both compounds blocked TNF-induced activation of Rap1A, a phox-associated guanosine triphosphatase that is regulated by cAMP. Thus, TNF turns on phox through a Ca2+-triggered, sAC-dependent process that may involve activation of Rap1A. This pathway may offer opportunities to suppress oxidative damage during inflammation without blocking antimicrobial function.

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---Logging off of STN---

Connection closed by remote host
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Unable to generate the STN prompt.
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